1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 2, Randomized, Double-blind, Placebo-controlled, 6-Week, Parallel-design Study of the Efficacy and Safety of VX-150 in Treating Subjects With Pain Caused by Small Fiber Neuropathy

Vertex Study Number: VX16-150-102

[redacted]

EudraCT Number: 2017-001042-10

Date of Protocol: 25 May 2018 (Version 5.0)

Vertex Pharmaceuticals Incorporated
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2 PROTOCOL SYNOPSIS

Title A Phase 2, Randomized, Double-blind, Placebo-controlled, 6-Week, Parallel-design Study of the Efficacy and Safety of VX-150 in Treating Subjects With Pain Caused by Small Fiber Neuropathy

Brief Title A Study to Evaluate the Efficacy and Safety of VX-150 in Treating Subjects With Pain Caused by Small Fiber Neuropathy

Clinical Phase and Clinical Study Type Phase 2 efficacy and safety

Objectives

Primary Objective:

To evaluate the efficacy of VX-150 for the treatment of pain caused by small fiber neuropathy

Secondary Objectives:

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

Endpoints

Primary Endpoint:

Change from baseline in the weekly average of daily pain intensity on the 11-point numeric rating scale (NRS), as reported in the daily diary, at Week 6

Secondary Endpoints:

- Proportion of subjects with ≥30% reduction in the weekly average of daily pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6
- Proportion of subjects with ≥50% reduction in the weekly average of daily pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6
- Change from baseline in the Daily Sleep Interference Scale (DSIS) at Week 6
- Proportion of subjects categorized as improved at Week 6 on the patient global impression of change (PGIC) assessment
- Change from baseline in pain intensity on the 11-point NRS, as reported at study visits, at Week 6
- Plasma PK parameters of VRT-1207355 and the metabolite VRT-1268114
- Safety and tolerability based on the Columbia Suicide Severity Rating Scale (C-SSRS), incidence and type of adverse events (AEs), changes from baseline in clinically significant laboratory test results, vital signs, and ECGs at each visit

[redacted]

Number of Subjects Up to approximately 114 subjects

Study Population Males and females between the ages of 18 and 80 years, inclusive

Investigational Drug

Active substance: VX-150

Activity: Na_v 1.8 blocker

Strength and route of administration: 1250 mg total dose daily, administered as 250-mg capsules orally

Study Duration

From Day -7 to last day of Safety Follow-up Visit, each subject will participate in the study for approximately 11 weeks.

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Up to approximately 114 subjects with small fiber neuropathy will be randomized 1:1 to VX-150 or placebo. Randomization will be stratified by sex and diagnosis of diabetes. Subjects with diabetes will not exceed approximately 60% of the total number of subjects. Subjects with diabetes and HbA1c ≥8% and <11% at screening will not exceed approximately 20% of the total number of subjects.

This study will include:

- A 7-day Run-in Period to establish the baseline NRS pain score
- A 6-week Treatment Period
- A 28-day Safety Follow-up Period

Assessments

Efficacy: NRS, DSIS, PGIC, [redacted]

Safety: AEs, C-SSRS, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, and physical examinations (PEs).

PK: Plasma PK parameters of VRT-1207355 and VRT-1268114

[redacted]

Statistical Analyses

The primary efficacy endpoint is the change from baseline in the weekly average of daily pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6.

The primary analysis of the primary endpoint will be a within-group treatment comparison in the VX-150 treatment group. The analysis will be conducted using a mixed-effects model for repeated measures (MMRM). The between-group treatment comparison will also be generated using the same MMRM.

The model will include the change from study baseline in the weekly average of daily NRS pain score as the dependent variable; treatment, sex, diagnosis of diabetes, week, and treatment-by-week interaction as fixed effects; subject as a random effect; and baseline pain intensity score as a covariate. In the model, week will be treated as a class variable, and an unstructured covariance matrix will be assumed to model the within-subject variability.

The estimated mean and corresponding 95% CI for VX-150 will be provided for the within-group change. The CI will first be used to facilitate the comparison with 0; this will be followed by a comparison with 0.8. In addition, the estimated mean and corresponding 95% CI for the between-group difference will be provided.

3 SCHEDULE OF ASSESSMENTS

Schedules of Assessments are shown in Table 3-1 and Table 3-2.

Table 3-1 Study VX16-150-102: Screening

Event/Assessment	Screening[a] Day -28 to Day -1
Outpatient visit	X
Informed consent form (ICF)	X
Inclusion/exclusion criteria	X
Demographics	X
Medical history	X
History of drug and alcohol use	X
Weight, height, and body mass index (BMI)[b]	X
Vital signs[c]	X
Physical examination	X
Standard 12-lead electrocardiogram (ECG)[d]	X
Serum β-hCG (all female subjects)	X
Serum follicle-stimulating hormone (FSH)[e]	X
Serology (HBsAg, HCV, and HIV 1/HIV 2)	X
Serum chemistry[f]	X
Hematology[f]	X
Coagulation[f]	X
HbA1c[g]	X
Thyroid function test	X
Methylmalonic acid	X
Vitamin B12	X
Urinalysis	X
Drug and alcohol testing	X
Skin biopsy	X
Nerve conduction studies (NCS)	X
Education on appropriate expectations for being in a clinical study and reporting pain	X
11-pt numeric rating scale (NRS) pain score via daily diary from Days -7 through -1[h]	X

[a] Subjects must discontinue all treatment for neuropathic pain (including medications, supplements, and non-pharmaceutical therapies) by Day -14 (see Section 9.4.1).
[b] Weight and height will be measured with shoes off.
[c] Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) will be collected after the subject has been seated or supine for at least 5 minutes and before any 12-lead ECG assessment or blood sampling.
[d] 12-lead ECGs will be performed after subjects have been supine for at least 5 minutes. 12-lead ECGs will be done after vital signs and before any procedures that may affect heart rate (e.g., blood sampling).
[e] Serum FSH is required for suspected postmenopausal female subjects only.
[f] Blood samples will be collected for clinical laboratory assessments following a fast of at least 4 hours.
[g] HbA1c will only be assessed for subjects with diabetes.
[h] Subjects will report their average daily pain during the last 24 hours on the NRS.

Table 3-1 Study VX16-150-102: Screening

Event/Assessment	Screening[a] Day -28 to Day -1
Prior medications taken for the treatment of neuropathic pain[i]	X
Prior and concomitant medications[j]	Continuous from signing of ICF through Safety Follow-up Visit
Treatments and procedures	Continuous from signing of ICF through Safety Follow-up Visit
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit

[i] All medications previously taken for the treatment of neuropathic pain will be recorded. Subjects will also indicate whether the medications were discontinued, and if so, the reason for discontinuation.

[j] All medications taken within 28 days before screening through the Safety Follow-up Visit will be recorded.

Table 3-2 Study VX16-150-102: Run-in Period, Treatment Period, and Safety Follow-up Visit

Event/Assessment	Day -7 (During Screening)	Day 1	Day 7 (± 1 Day)	Week 3 (± 3 Days)	Week 6 (± 3 Days)	ETT Visit[a]	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug
Clinic visit	X	X	X	X	X	X	X
Randomization		X					
Study drug dosing[b]			Day 1 through Week 6				
Weight[c]	X	X			X	X	X
Vital signs[d]	X	X	X	X	X	X	X
Standard 12-lead ECG[e]	X	X	X			X	X
Physical examination[f]		X					
Neurological examination			X	X	X	X	X
Urinalysis		X				X	X
Drug and alcohol testing	X			X	X	X	
Pregnancy test[g]	serum	urine	urine	urine	serum	serum	serum
Coagulation					X	X	X
Hematology		X		X	X		X
Serum chemistry		X		X	X		X
PK sampling[h]			X	X	X	X	
[redacted]							

[a] If the subject prematurely discontinues study treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (± 7) days after their last dose of study drug. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

[b] Study drug (VX-150 or placebo) will be administered daily under fasted conditions. The Day 7 dose will be administered at the clinic.

[c] Weight will be measured with shoes off.

[d] Vital signs will be collected after the subject has been at rest (seated or supine) for at least 5 minutes.

[e] Standard 12-lead ECGs will be performed after subjects have been supine for at least 5 minutes. 12-lead ECGs will be done after vital signs and before any procedures that may affect heart rate (e.g., blood sampling).

[f] The neurological component of the Day 1 complete physical examination includes sensory testing conducted with the bedside sensory testing kit (BSTK). Symptom-directed physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

[g] Pregnancy tests will only be performed for female subjects of childbearing potential.

[h] With the exception of Day 7, PK samples will be collected at any time during the study visit. On Day 7, 2 PK samples will be collected: 1 sample before the dose of study drug, and 1 sample 1 to 4 hours after the dose of study drug.

Table 3-2 Study VX16-150-102: Run-in Period, Treatment Period, and Safety Follow-up Visit

Event/Assessment	Day -7 (During Screening)	Day 1	Day 7 (± 1 Day)	Week 3 (± 3 Days)	Week 6 (± 3 Days)	ETT Visit[a]	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug
11-pt numeric rating scale (NRS) pain score via daily diary[i]	Day -7 through Week 6 or ETT Visit via daily diary						
11-pt NRS pain score at study visits[j]	X	X	X	X	X	X	X
Daily Sleep Interference Scale (DSIS)[k]	Day -7 through Week 6 or ETT Visit via daily diary						
Patient global impression of change (PGIC)		X	X	X	X	X	X
[redacted]							
Columbia Suicide Severity Rating Scale (C-SSRS)		X	X	X	X	X	X
Study drug count			X	X	X	X	
Medications review	Continuous from signing of the ICF through the Safety Follow-up Visit						
Concomitant treatments and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit						
Adverse events	Continuous from signing of the ICF through the Safety Follow-up Visit						

i From Day -7 through Week 6 or ETT Visit, subjects will report their average daily pain during the last 24 hours on the NRS each evening. Subjects will also report their current pain immediately before each administration of rescue medication.

j At study visits, subjects will report their average pain during the last 24 hours on the NRS.

k From Day -7 through Week 6 or ETT Visit, subjects will report each morning on the previous night's sleep using the DSIS.

4 TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ANCOVA	analysis of covariance
AUC	area under the concentration versus time curve
AUC_{0-24}	area under the concentration versus time curve from the time of dosing to 24 hours
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BSTK	bedside sensory testing kit
C_{max}	maximum observed concentration
CI	confidence interval
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DDI	drug-drug interaction
DSIS	Daily Sleep Interference Scale
ECG	electrocardiogram
EDC	electronic data capture
ETT	Early Termination of Treatment
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	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonization
IEC	independent ethics committee
IRB	institutional review board
IXRS	interactive response system in which X represents voice or web, such as IWRS
max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum value
MMRM	mixed-effects model for repeated measures
MRC	Medical Research Council
n	number of subjects

Abbreviation	Definition
Na_v	voltage-gated sodium channels
NCS	nerve conduction studies
[redacted]	[redacted]
NRS	numeric rating scale
PCS	potentially clinically significant
PD	pharmacodynamic, pharmacodynamics
PE	physical examination
PGIC	patient global impression of change
PK	pharmacokinetic, pharmacokinetics
PR	PR interval, segment
prn	as needed
qd	daily
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SET	study execution team
[redacted]	[redacted]
[redacted]	[redacted]
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SI	SI units (International System of Units)
TEAE	treatment-emergent adverse event
US	United States
WHO-DDE	World Health Organization-Drug Dictionary Enhanced

5 INTRODUCTION

Pain is the most common symptom 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 have 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] Opioid pain medications have a high abuse liability with approximately 16,000 annual deaths in the US and between 10,000 and 20,000 annual deaths in Europe due to overdose.[2, 3] In addition, opioid-induced hyperalgesia also limits the long-term use of opioids. While the incidence of opioid-induced hyperalgesia is not known, it is encountered regularly in clinical practice and creates significant challenges in pain management.[4] The limited treatment options for pain, particularly chronic pain indications, 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.[5-7] 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 some patients with painful small fiber neuropathy.[8-10] This channel has been identified as a target for analgesia[11] and selective $Na_v1.8$ blockers, 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.

To date, 4 Phase 1 clinical studies have been completed with VX-150. [redacted]

One Phase 2a study has completed dosing; Study VX15-150-101 (Study 101) is a proof of concept study to evaluate efficacy in patients with osteoarthritis pain. Overall, VX-150 has been well tolerated without any safety concerns. Additional details of the VX-150 development program are available in the VX-150 Investigator's Brochure.[12]

Small fiber neuropathy is a distinct clinical condition caused by diseases affecting peripheral small nerve fibers (Aδ- and C-fibers). Common symptoms include burning pain in the feet and

evoked pain (e.g., pressure and touch allodynia). Diagnosis is defined as possible, probable, and definite based on the combination of symptoms, signs, evidence of large sensory nerve fiber function integrity by nerve conduction studies (NCS) and abnormal skin biopsy or quantitative sensory testing.[13, 14] By inhibiting $Na_v1.8$ in the peripheral nerve fibers, VX-150 has the potential to treat pain caused by hyperexcitability of the damaged or diseased nerves.
Study VX16-150-102 is a proof of concept study that will evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of VX-150 in the treatment of neuropathic pain in subjects with small fiber neuropathy.

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the efficacy of VX-150 for the treatment of pain caused by small fiber neuropathy

6.2 Secondary Objectives

- To evaluate the safety and tolerability of VX-150
- To evaluate the PK of VRT-1207355 and the metabolite VRT-1268114

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Change from baseline in the weekly average of daily pain intensity on the 11-point numeric rating scale (NRS), as reported in the daily diary, at Week 6

7.2 Secondary Endpoints

- Proportion of subjects with ≥30% reduction in the weekly average of daily pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6
- Proportion of subjects with ≥50% reduction in the weekly average of daily pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6
- Change from baseline in the Daily Sleep Interference Scale (DSIS) at Week 6
- Proportion of subjects categorized as improved at Week 6 on the patient global impression of change (PGIC) assessment
- Change from baseline in pain intensity on the 11-point NRS, as reported at study visits, at Week 6
- Plasma PK parameters of VRT-1207355 and the metabolite VRT-1268114
- Safety and tolerability based on the Columbia Suicide Severity Rating Scale (C-SSRS), incidence and type of AEs, changes from baseline in clinically significant laboratory test results, vital signs, and ECGs at each visit

[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 for the study.

8.1 Inclusion Criteria

1. Subject will sign and date an informed consent form (ICF)
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures
3. Subjects (male and female) will be between the ages of 18 and 80 years, inclusive.
4. Body mass index (BMI) of $\geq$18.0 kg/m^2
5. Diagnosis of small fiber neuropathy, as per European Federation Neurological Societies (EFNS)/American Academy of Neurology (AAN) guidelines, with pain for at least 3 months prior to screening
6. Reduction below the 5th percentile of sex and age-adjusted normal values in epidermal nerve fiber density on punch skin biopsy at the distal site of the leg performed at screening
7. Presence of sural nerve responses
8. Average NRS score between $\geq$4 and $\leq$9 reported in the daily diary on Days -7 through -1

8.2 Exclusion Criteria

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. Exposure to neurotoxic drugs (i.e., chemotherapy) since diagnosis of small fiber neuropathy. Untreated or uncontrolled connective tissue disorders, sarcoidosis, Sjögren's syndrome, amyloidosis, Fabry's disease, celiac disease, Lyme disease, autoimmune disorders (i.e., as assessed by anti-nuclear antibodies, rheumatoid factor, sedimentation rate, and/or lupus anti-coagulant) including myasthenia gravis and Guillain-Barre syndrome, which in the opinion of the investigator makes the subject unsuitable for inclusion in this study.
3. A known or clinically suspected infection with human immunodeficiency virus or hepatitis B or C viruses

4. Current clinically significant liver or kidney dysfunction
5. Current uncontrolled thyroid dysfunction
6. Subjects with a diagnosis of diabetes who have any 1 of the following criteria:
   - HbA1c ≥11% at screening
   - are not stabilized on oral hypoglycemics and/or subcutaneous insulin or diet, in the opinion of the investigator
   - evidence of ulcers or severe nephropathy resulting from their diabetes
   - advanced retinopathy, defined as greater than State 3 (moderate non-proliferative diabetic retinopathy)[15]
   - history of a clinical atherosclerotic event, such as myocardial infarction or stroke
7. History of cardiac dysrhythmias requiring anti-arrhythmia treatment(s); or history or evidence of abnormal ECGs that in the opinion of the investigator or medical monitor would preclude the subject's participation in the study
8. Standard 12-lead ECG demonstrating QTc >450 msec at screening. If QTc exceeds 450 msec, the ECG will be repeated 2 more times, and the average of the 3 QTc values will be used to determine the subject's eligibility.
9. Concomitant severe pain conditions (i.e., low back pain, radiculopathy, severe bone and musculoskeletal disorders) which may impair self-assessment of pain due to small fiber neuropathy
10. Abnormal laboratory results indicative of any significant medical disease that, in the opinion of the investigator, would preclude the subject's participation in the study
11. 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
12. Female subjects who are pregnant, nursing, or planning to become pregnant during the study or within 90 days after the last study drug dose
13. 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
14. Use of restricted medication or food within the specified duration before the first dose of study drug, as defined in Table 9-1
15. Alcohol, analgesic/opioid, and/or illicit drug abuse as defined by the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, in the last 12 months before screening, or a positive test for drugs of abuse at screening
    - A positive drug screen for a known concomitant medication that is not otherwise exclusionary (e.g., benzodiazepines) will not disqualify subjects; however, marijuana and marijuana derivatives will not be allowed

16. 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

9 STUDY IMPLEMENTATION

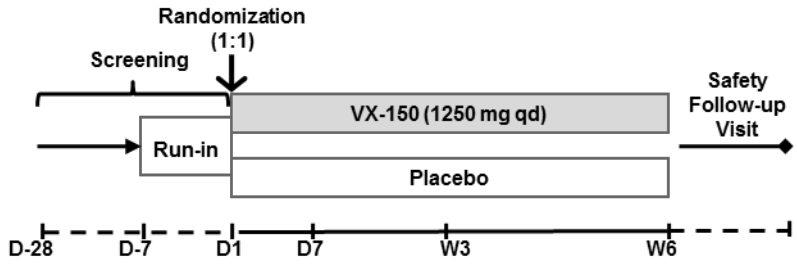
9.1 Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter study (Figure 9-1). Up to approximately 114 subjects with small fiber neuropathy will be randomized 1:1 to VX-150 or placebo. Randomization will be stratified by sex and diagnosis of diabetes. Subjects with diabetes will not exceed approximately 60% of the total number of subjects. Subjects with diabetes and HbA1c ≥8% and <11% at screening will not exceed approximately 20% of the total number of subjects.

This study will include:

- A 7-day Run-in Period to establish the baseline NRS pain score
- A 6-week Treatment Period
- A 28-day Safety Follow-up Period

Figure 9-1 Schematic of Study Design



D: Day; qd: daily; W: Week

9.1.1 Screening

Screening Visit assessments are listed in Table 3-1.

Screening will occur within 28 days before administration of study drug. The Screening Visit can occur between Days -28 and -8. 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). During screening, subjects will discontinue their current pain treatments as outlined in Section 9.4.1. Subjects will be permitted to take acetaminophen as needed (prn), following the guidelines in Section 9.4.1.

Subjects will be instructed during screening on appropriate expectations around their participation in a clinical study and the importance of consistently and accurately reporting their pain throughout the study (e.g., "Participating in a Research Study" and "Reporting Your Pain", Analgesic Solutions, Natick, MA). Review of these educational materials may be repeated for

some or all subjects depending on findings of an ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level).

Subjects who do not meet the eligibility criteria may not be rescreened, with the following exceptions, all of which require medical monitor approval:

- 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
- Subjects who met all eligibility criteria but are not randomized for administrative reasons (e.g., interactive web or voice response system [IXRS] is temporarily inaccessible or nonfunctional, or study drug is not available at the study site)

Any subject granted approval by the medical monitor for any of the exceptions listed above may have the screening window extended by 1 week before needing to undergo any rescreening assessments. If more than 35 days have elapsed from screening before first dose of study drug, all screening assessments, except skin biopsy and NCS, need to be repeated. 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). In all cases, the medical monitor must authorize retesting.

9.1.2 Run-in Period

Run-in Period assessments are listed in Table 3-2 and will occur from Day -7 through Day -1 during screening. During the Run-in Period, subjects will report their average pain as described in Section 11.5 to establish the baseline NRS pain score. Subjects will follow the pain treatment restrictions outlined in Section 9.4.1. Subjects will be permitted to take acetaminophen prn, following the guidelines in Section 9.4.1, as a rescue medication for intermittent pain.

9.1.3 Treatment Period

Treatment Period assessments are listed in Table 3-2.

All study periods will be conducted as described previously in Section 9.1. Dosing details are given in Section 9.3.2. During the Treatment Period, subjects will follow the pain treatment restrictions outlined in Section 9.4.1. Subjects will be permitted to take acetaminophen prn, following the guidelines in Section 9.4.1, as a rescue medication for intermittent pain.

Subjects who prematurely discontinue study drug treatment will remain in the study from the time of discontinuation of study drug treatment through the last scheduled study visit, and complete assessments for all study visits, as described in Section 9.1.5.

9.1.4 Follow-up

Subjects will have a Safety Follow-up Visit 28 (± 7) days after the last study drug dose. Safety Follow-up Visit assessments are listed in Table 3-2.

9.1.5 Early Termination of Treatment

If the subject prematurely discontinues study drug treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the subject decides to terminate study drug treatment.

Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 days (± 7) days after their last dose of study drug. The assessments performed at the Safety Follow-up Visit are listed in Table 3-2. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

If the subject withdraws consent for the study, no further evaluations should be performed, and no additional data should be collected. Vertex Pharmaceuticals Incorporated may retain and continue to use any data collected before such withdrawal of consent.

9.2 Method of Assigning Subjects to Treatment Groups

An interactive web response system (IWRS) 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 (SET).

9.3 Rationale for Study Design and Study Drug Regimens

9.3.1 Study Design

This study is designed to evaluate the efficacy of VX-150 for treatment of pain in subjects with small fiber neuropathy. The randomized, double-blind study design will limit observer bias, minimize carryover effect and reduce the possibility for unblinding. The potential for a carryover effect is due either to the potential subjective nature of pain measurements and/or the effect of treatment with VX-150. For the primary endpoint, daily NRS pain scores will be averaged over a weekly period to reduce the impact on the analyses of individual high or low pain scores.

9.3.2 Study Drug Dose and Duration

The VX-150 dose selected for this study will be 1250 mg qd administered under fasting conditions using a capsule formulation. [redacted]

9.3.3 Rationale for Study Assessments

11-point NRS: Pain intensity is the FDA-recommended efficacy endpoint for studies of pain drugs.[16, 17] This evaluation is a standard pain assessment scale used in many pain registration studies. The 11-point scale ranges from 0 (no pain) to 10 (worst imaginable pain).

The minimum clinically important difference for an individual is considered to be a 1-point change from baseline, approximately equivalent to 15% to 20% improvement. Changes of 2 points are considered equivalent to approximately 30% to 36% improvement (i.e., meaningful improvement); and changes of ≥4 points are considered equivalent to ≥50% improvement (i.e., substantial improvement).[17, 18]

DSIS: Pain frequently interferes with sleep and sleep is important to quality of life. The FDA recommends evaluating the effect of analgesics on sleep.[16, 17] DSIS is commonly used in neuropathic pain studies and is assessed on an 11-point NRS. The 11-point scale ranges from 0 (none) to 10 (severe).

PGIC: The PGIC is commonly used in neuropathic pain studies, and the IMMPACT group recommends it as a core outcome measure for chronic pain studies.[17] There is some evidence that PGIC may be more sensitive in neuropathic pain studies than pain intensity assessments because it may assess additional quality of life measures.[18] The assessment consists of a single item on a 7-point scale from 1 (very much improved) to 7 (very much worse).

[redacted]

C-SSRS: The FDA recommends the evaluation of suicidality in clinical studies. The C-SSRS evaluates this through a series of questions about suicidal thoughts and behaviors.

NCS: NCS are a standard assessment for the diagnosis of small fiber neuropathy. Normal NCS are part of the diagnostic criteria for small fiber neuropathy. NCS will be performed to rule out large nerve fiber involvement.

Skin biopsy: Punch skin biopsy will be performed at screening to confirm the diagnosis of small fiber neuropathy based on the epidermal nerve fiber density. Skin biopsy is considered the gold standard for diagnosis of small fiber neuropathy.

[redacted]

9.4 Study Restrictions

Study restrictions are summarized in Table 9-1.

Table 9-1 Study Restrictions

Restricted Medication/Food/Activity[a]	Timing of Restriction	
	From (minimum)	**To**
Other investigational drugs or devices	1 month before first study drug dose, or time determined by local requirements; whichever is longest	Completion of Safety Follow-up Visit assessments
[redacted]		
Sensitive CYP3A substrates	7 days before first study drug dose	Completion of Safety Follow-up Visit assessments
Medications with potential effects on sodium channel function, including lamotrigine, carbamazepine, oxcarbazepine, mexiletine, amitriptyline, and topical agents	14 days before first study drug dose	Completion of Week 6 or ETT Visit assessments
Any use of marijuana or marijuana derivatives	14 days before first study drug dose	Completion of Week 6 or ETT Visit assessments
Capsaicin patch	90 days before first study drug dose	Completion of Week 6 or ETT Visit assessments
Gabapentin and pregabalin	14 days before first study drug dose	Completion of Week 6 or ETT Visit assessments
All treatments for pain (as outlined in Section 9.4.1)	14 days before first study drug dose	Completion of Week 6 or ETT Visit assessments
Vitamin E supplements	7 days before first study drug dose	Completion of Safety Follow-up Visit assessments
[redacted]		

Table 9-1 Study Restrictions

Restricted Medication/Food/Activity[a]	Timing of Restriction	
	From (minimum)	To
[redacted]		
Grapefruit/grapefruit juice, pomelos, star fruit, Seville oranges, marmalade	7 days before first study drug dose	Completion of Week 6 or ETT Visit assessments

[a] Refer to the Study Reference Manual for a more complete list of prohibited/restricted medications.

All medications taken from 28 days before screening through the Safety Follow-up Visit will be recorded with indication, route of administration, and start and stop dates of administration. All subjects will be questioned about medications at each study visit.

9.4.1 Treatments for Pain

- Subjects will abstain from all treatment for neuropathic pain (including medications, supplements, and non-pharmaceutical therapies) from 14 days before the first dose of study drug through the Week 6 Visit (or ETT Visit, if applicable). Subjects taking aspirin for cardiovascular health may remain on their stable dose throughout the study.
- Acetaminophen will be permitted as a pain rescue medication prn throughout the study. Subjects will be permitted to take 500 mg every 4 to 6 hours prn, up to a maximum of 2500 mg in any 24-hour period prn. Subjects will record rescue medication use, and their current pain on the NRS immediately before each administration of rescue medication.
- There are no restrictions on pain treatments between the completion of the Week 6 Visit (or ETT Visit, if applicable) and the Safety Follow-up Visit.

9.4.2 Additional Dietary Restrictions

Subjects will abstain from all food and drink (except water) at least 4 hours before the Screening Visit safety laboratory evaluations.

Subjects will abstain from all food and drink (except water, black coffee, or tea) at least 2 hours prior to dosing and for 2 hours after dosing. [redacted]

9.5 Administration

VX-150 will be administered 1250 mg qd orally.

- Subjects will abstain from all food and drink (except water, black coffee, or tea) at least 2 hours prior to dosing and for 2 hours after dosing. [redacted]
- Subjects will take study drug at approximately the same time each day and 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.
- If a subject forgets to take a dose and remembers within 12 hours (before the halfway point of the dosing interval), they will take the dose at that time and resume their normal schedule for the following dose.
- If a subject forgets to take a dose and remembers more than 12 hours after the missed dose, they will skip that dose and resume their normal schedule for the following dose.
- On days of the study visits where a PK sample is collected, the following will be recorded for each of the 2 doses taken before the visit:
  - date and time the dose was taken
  - amount taken
  - whether the dose was taken with or without food
- The Day 7 dose will be administered at the clinic. At the Day 7 clinic visit, 1 PK sample will be collected before the dose of study drug, and 1 PK sample will be collected 1 to 4 hours after the dose of study drug.

9.6 Dose Modification for Toxicity

If any unacceptable toxicity arises, individual subjects will discontinue dosing (Section 9.1.5).

9.7 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. If a subject has been withdrawn from study drug treatment, the subject will continue to be followed, provided the subject has not withdrawn consent.

Subjects who discontinue study treatment early should continue to return for safety assessments, as noted in Section 9.1.5.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit, if applicable (see Section 9.1.5), and follow up with the subject regarding any unresolved AEs.

If the subject withdraws consent for the study, no further evaluations will be performed and no additional data will be collected. Vertex may retain and continue to use any data collected before such withdrawal of consent.

9.8 Replacement of Subjects

Subjects who withdraw or are withdrawn for nonsafety reasons during the study drug treatment period 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.

10.2 Packaging and Labeling

Vertex will supply the 250-mg VX-150 and placebo capsules. 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. 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	Formulation/ Route	Dosage	Packaging
VX-150	Capsule/Oral	1250 mg, qd	Supplied as 250-mg capsules
VX-150 placebo	Capsule/Oral	None	Supplied as capsules

10.4 Drug Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of (1) study drug received; (2) study drug dispensed to the subjects; and (3) study drug returned by the subjects. Subjects will be instructed to return all unused materials associated with the study drug to the site. These materials will be retained at the site according to instructions provided by Vertex or its designee until inventoried by the study monitor. The study monitor will review study drug records and inventory throughout the study.

10.5 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subjects until the study monitor has performed drug accountability. At the end of the study, the study monitor will provide instructions as to the disposition of any unused investigational product. If the study monitor authorizes destruction at the study site, the investigator will ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Vertex. Destruction will be adequately documented.

10.6 Compliance

Drug accountability will be assessed at each clinic visit by counting returned dosage units. Discrepancies will be discussed with the subject and recorded in the source documents. If subjects demonstrate continued noncompliance of study drug dosing despite educational efforts,

the investigator will contact the medical monitor to discuss discontinuing the subject from the study.

10.7 Blinding and Unblinding

This will be 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 (or female partner of the male subject) and the fetus in the event of a pregnancy
- An unblinded pharmacist at the contract research organization (CRO) for dispensing study drug
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy serious adverse event (SAE) processing and reporting regulations
- External vendor (unblinded) statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IXRS Management for IXRS oversight and system administration
- Vertex Clinical Supply Chain
- The bioanalytical laboratory/vendor personnel managed by Vertex Bioanalysis

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

A Vertex Bioanalysis Representative will be unblinded to allow real time review of bioanalytical data. This individual, however, will not be a member of the SET, and will not interact with the clinical research unit (CRU) or study personnel.

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 data set is being provided for preliminary analysis. This individual, however, will not be a member of the SET, and will not interact with the CRU or study personnel. Masked IDs will be used for these analyses.

10.7.2 Unblinding

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

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.

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), 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 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

11.1 Timing of Assessments

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

11.2 Subject and Disease Characteristics

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

11.3 Pharmacokinetics

11.3.1 Blood Sampling

For the evaluation of plasma concentrations of VRT-1207355 and VRT-1268114, blood samples will be collected from all subjects according to the Schedule of Assessments (Table 3-2).

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

Blood samples collected from subjects administered placebo will not be routinely analyzed.

The following will be recorded before PK sample collection: date and time the dose was taken, amount taken, time since they last ate, and a description of the contents of their meal.

11.3.2 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.

11.3.3 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]

11.5 Efficacy

11-point NRS: Pain intensity will be evaluated using the 11-point NRS. From Day -7 through Week 6, subjects will report their average daily pain during the last 24 hours on the NRS via electronic diary. [redacted] At study visits, subjects will also report their average pain during the last 24 hours on the NRS. The NRS scores from the daily diary will be used in the primary endpoint analysis, and the proportion of subjects with ≥30% and ≥50% reduction in weekly average scores as reported in the daily diary and at study visits will be used in the secondary endpoint analyses.

DSIS: The DSIS will be completed each morning in an electronic diary to describe how pain interfered with the subject's sleep.

PGIC: The PGIC will be completed at study visits to quantify the change in subjects' overall status.

[redacted]

11.6 Safety

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

11.6.1 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.

11.6.2 Clinical Laboratory Assessments

At the Screening Visit, blood specimens will be collected for safety laboratory tests following at least a 4-hour fast. At other time points, fasting is only required with respect to dosing (see Section 9.4.2 and Section 9.5). On Day 1, blood samples will be collected before the first dose of study drug. At all other scheduled visits, these samples will be collected at any time during the clinic visit.

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 11-1.

Table 11-1 Safety Laboratory Test Panels

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

Note: Screening Visit blood draws will be done after a minimum 4-hour fast.

[a] If urinalysis results are positive for leukocyte esterase, nitrite, 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.

Additional tests at screening: The following additional tests will be performed during screening to assess eligibility:

- Serum beta-human chorionic gonadotropin (β-hCG) for all female subjects
- Serum follicle-stimulating hormone (FSH) for suspected postmenopausal female subjects only. Levels will be within the laboratory's range for postmenopausal levels for subjects to be considered of non-childbearing potential.
- Serology includes testing for hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (HCV) and human immunodeficiency viruses 1 and 2 (HIV 1/HIV 2).
- HbA1c (for subjects with diabetes only)
- Thyroid function test
- Methylmalonic acid
- Vitamin B12

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.

Pregnancy testing for female subjects of childbearing potential (as defined in Section 11.6.6.1):

Pregnancy test results must be negative for female subjects of childbearing potential to receive study drug.

During treatment, if a urine or serum pregnancy test is positive, all study drug dosing will stop and the pregnancy will be confirmed with a serum β-hCG test. If confirmed, the pregnancy will be reported and the subject will be permanently withdrawn from study drug dosing as discussed in Section 11.6.6.2. If a pregnancy test is positive, the procedures outlined in Section 11.6.6.2 will be followed.

Drug and alcohol testing: Opiates, methadone, amphetamines/methamphetamines, cannabinoids, cocaine, barbiturates, and benzodiazepines will be assessed by a urine test. Alcohol will be assessed by a blood, urine, or breath test. Subjects may undergo random drug and alcohol testing if deemed appropriate by the investigator. Drug and alcohol test results must be negative for all subjects to receive study drug.

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

For purposes of study conduct, only laboratory tests done in the central laboratory may be used. 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.

11.6.3 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 will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

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

The neurological component of the Day 1 complete PE includes the bedside sensory testing kit (BSTK) for the purpose of standardized assessment and phenotyping of subjects' pain, using the usual components of the neurological examination. Included in the BSTK are standard tools used in assessment of the neurological system, including a turning fork, foam brushes, von Frey fiber, and safety pins.

A focused neurological examination will be performed at all other visits after the Day 1 Visit. The focused neurological examination includes: testing of strength via the Medical Research Council (MRC) rating scale, reflexes, sensation to light touch, and pin prick.

Vital signs include blood pressure (systolic and diastolic), temperature (oral), pulse rate, and respiration rate. These will be assessed following at least a 5-minute rest in the seated or supine position.

11.6.4 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout according to the Schedule of Assessments (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 subject will be instructed to rest in the supine position for at least 5 minutes before having an ECG performed.
- The ECG will be performed before any procedures that may affect heart rate, such as blood sampling.

The ECG traces will be manually read at the study site at the Screening Visit and Safety Follow-up Visit. 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 Visit will be recorded as AEs.

To ensure safety of the subjects, a qualified individual at the study site will make comparisons to baseline measurements. If the 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.

11.6.5 Columbia Suicide Severity Rating Scale

The C-SSRS will be performed according to the Schedule of Assessments (Table 3-2).

11.6.6 Contraception and Pregnancy

11.6.6.1 Contraception

Following the recommendations outlined by the Heads of Medicines Agencies Clinical Trial Facilitation Group, study participation requires a commitment from the subject that he/she and his/her partner use **1 acceptable method of contraception** that is listed in Table 11-2 from the Screening Visit through 90 days after the last dose of study drug. Male subjects must also not donate sperm from the 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 11-2 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 first dose of study drug	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) used alone or in combination with cap, diaphragm, or sponge with spermicide	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 (non-hormone releasing) for at least 90 days before the first dose of study drug	Yes	Yes
Hormonal contraceptives, if successfully used for at least 60 days before the first dose of study drug	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 acceptable form of contraception due to the potential for drug-drug interactions between hormonal contraceptives and VX-150 resulting in reduced exposure and contraception failure.

11.6.6.2 Pregnancy

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

If a subject or the female partner of a male subject becomes pregnant while participating in the study, 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 Safety 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

This section presents a summary of the planned analyses for this protocol. Statistical analysis details will be provided in the statistical analysis Plan (SAP), and clinical pharmacologic analysis details will be provided in the clinical pharmacology analysis plan (CPAP), both of which will be finalized before the clinical data lock for the study and treatment unblinding.

12.1 Sample Size and Power

The primary efficacy endpoint is the change from baseline in the weekly average of daily pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6. The primary analysis of the primary efficacy endpoint will be a within-group treatment comparison in the VX-150 treatment group. The 95% CI for the within-group change will be used to evaluate if there is any significant change from baseline (within-group change against 0). Additional analyses will include an evaluation of this within-group change against 0.8, an expected change from the placebo group, and a 95% CI for the between-group comparison of change from baseline.

Assuming a within-group change of 0.8 for placebo and a between-group treatment difference of 1.25[22-24], the expected within-group change for VX-150 is 2.05. With an SD of 2.08, the power for the 95% CI for the within-group change to rule out 0 or 0.8 is summarized in Table 12-1 for 25, 35, or 45 evaluable subjects per group. The power for the 95% CI for the between-group treatment difference to rule out 0 is also provided. In order to allow for withdrawal of up to 20% of randomized subjects over 6 weeks of treatment, the study will enroll and randomize a minimum of approximately 62 subjects (25 evaluable subjects per group) and up to approximately 114 subjects (45 evaluable subjects per group) in total.

Table 12-1 Power for the 95% CIs for Within- and Between-group Changes

Number of Evaluable Subjects Per Group	Power for the 95% CI for the Within-group Change to Rule Out 0	Power for the 95% CI for the Within-group Change to Rule Out 0.8	Power for the 95% CI for the Between-group Treatment Difference to Rule Out 0
25	>99%	82%	55%
35	>99%	93%	70%
45	>99%	98%	81%

CI: confidence interval

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 is considered to be sufficient and interpretable.

12.3 Statistical Analysis

The primary objective of this study is to evaluate the efficacy of VX-150 in treating pain caused by small fiber neuropathy.

This section presents a summary of the planned statistical analyses of efficacy and safety. The Vertex Biometrics department will analyze the data derived from this study. Statistical Analysis System Version 9.2 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 SAP.

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, SE, median, minimum value (min), and maximum value (max). Categorical data will be summarized using counts and percentages.

Baseline value for the NRS daily diary scores and the DSIS will be defined as the average score from Day -7 to Day -1. For all other variables baseline will be defined as the most recent non-missing measurement 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 (i.e., completed Safety Follow-up Visit), 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, diagnosis of diabetes, and pain in the Run-in Period.

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 28 days before the Screening Visit and up to the Safety Follow-up Visit will be summarized by Preferred Name using the World Health Organization-Drug Dictionary Enhanced (WHO-DDE) for the FAS as frequency tables in 2 parts:

1. Prior medication: Medication that started before the first dose of study drug, regardless of when dosing of the medication ended.
2. 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

Exposure to study drug (i.e., duration of treatment) will be summarized for the FAS in terms of duration of treatment a subject received (in days), defined as the last day minus the first day of study drug plus 1.

Dosing compliance will be summarized for the FAS, and is calculated as the actual number of dosing occasions at which study drug was administered, as a percentage of the planned number of dosing occasions.

Duration of treatment and dosing compliance will be summarized by means of descriptive summary statistics.

12.3.3 Efficacy Analysis

Assessment of 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 change from baseline in the weekly average of daily pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6.

The primary analysis of the primary endpoint will be a within-group treatment comparison in the VX-150 treatment group. The analysis will be conducted using a mixed-effects model for repeated measures (MMRM). The between-group treatment comparison will also be generated using the same MMRM. The model will include the change from study baseline in the weekly average of daily pain intensity score as the dependent variable; treatment, sex, diagnosis of diabetes, week, and treatment-by-week interaction as fixed effects; subject as a random effect; and baseline pain intensity score as a covariate. In the model, week will be treated as a class variable, and an unstructured covariance matrix will be assumed to model the within-subject variability. The denominator degrees of freedom for the F-test for fixed effects will be estimated using the Kenward-Roger approximation.

The estimated mean and corresponding 95% CI for VX-150 will be provided for the within-group change. The CI will first be used to facilitate the comparison with 0; this will be followed by a comparison with 0.8. In addition, the estimated mean and corresponding 95% CI for the between-group difference will be provided.

12.3.3.2 Analysis of Secondary Efficacy Variables

Secondary endpoints are:

- Proportion of subjects with ≥30% reduction in the weekly average of daily pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6. This endpoint will be evaluated using descriptive statistics.

- Proportion of subjects with ≥50% reduction in the weekly average of daily pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6. This endpoint will be evaluated using descriptive statistics.
- Change from baseline in the DSIS at Week 6. The analysis of this endpoint will be similar to the primary analysis.
- Proportion of subjects categorized as improved at Week 6 on the PGIC assessment. This endpoint will be evaluated using descriptive statistics.
- Change from baseline in pain intensity on the 11-point NRS, as reported at study visits, at Week 6. The analysis of this endpoint will be similar to the primary analysis.

[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 (including coagulation studies)
- ECG outcomes
- Vital signs
- C-SSRS

Safety analyses will be 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, as well as by treatment group. AEs will be classified as pretreatment or treatment-emergent as follows:

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

Treatment-emergent AEs are defined as AEs that were reported or worsened on or after the start of study drug dosing through the Safety Follow-up Visit.

Only TEAEs will be summarized in tables. All summaries of TEAEs will be presented by the severity of the AE and 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.

AEs leading to death, SAEs, AEs leading to dose discontinuation, and study discontinuation will be listed separately. All AEs through the Safety Follow-up Visit 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 SI units. Hematology (including coagulation) and clinical chemistry results will be summarized by treatment group at each scheduled time point. The number and percentage of subjects with at least 1 potentially clinically significant (PCS) event will be summarized by treatment group at each scheduled time point. A listing containing individual subject laboratory measurements meeting the PCS criteria will be provided. For each subject in the listing, laboratory measurements at all time points will be included. The PCS criteria for clinical laboratory data will be provided in the SAP. Urinalysis results will be listed only in individual subject data listings. These results will not be summarized. 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 visit 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 ≤0 msec, >0 and ≤30 msec, >30 and ≤60 msec, and >60 msec, will be provided. 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 time point: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute). 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

Responses to the C-SSRS will be tabulated by treatment group.

12.3.5 Interim and IDMC Analyses

Not applicable.

12.4 Clinical Pharmacology Analysis

12.4.1 Pharmacokinetic Analysis

The PK parameters of VRT-1207355 and the metabolite VRT-1268114 will be described using summary statistics. Preliminary review and analyses of the drug concentrations may be done before database lock under the conditions of masked identifications of the subject concentrations.

Details of the analyses will be provided in the CPAP.

12.4.2 Pharmacodynamic Analysis

12.4.3 Pharmacokinetic/Pharmacodynamic Analyses

A population PK analysis of plasma concentration versus time data of VRT-1207355 and VRT-1268114 may be performed using a 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 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 ICF is signed until the following time points:

- 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 Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, the earliest of
  - 35 days after the last dose of study drug, or
  - the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (see Section 9.1.5)

All subjects will be queried, using nonleading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms will be identified as 1 overall event or diagnosis. All AEs for enrolled subjects will be recorded in the CRF and source document. AEs for subjects who are screened but not subsequently enrolled in the study 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 August 2015). 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 presented 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 study 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 shown 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 shown in Table 13-4.

Table 13-4 Classifications for Outcome of an AE

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

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, hospitalization, 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 in the study 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 Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through the Safety Follow-up Visit, regardless of causality, will be reported by the investigator to Vertex GPS. In addition, all SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours**.

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

13.1.2.3 Reporting Serious Adverse Events

The investigator is responsible for notifying the sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. 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]

Contact Telephone: [redacted]

13.1.2.4 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions involving the study drug(s) to all regulatory authorities 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/local 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 only be conducted 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 shall be limited to the site and the study physician and shall 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 study in the US, and in accordance with the Health Insurance Portability and Accountability Act and associated regulations ("HIPAA") an executed HIPAA authorization shall be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization shall 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.

13.3 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 study participant. 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 the CRFs, 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 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 #: VX16-150-102	Version #: 5.0	Version Date: 25 May 2018
Study Title: A Phase 2, Randomized, Double-blind, Placebo-controlled, 6-Week, Parallel-design Study of the Efficacy and Safety of VX-150 in Treating Subjects With Pain Caused by Small Fiber Neuropathy		

This Clinical Study Protocol has been reviewed and approved by the sponsor.

[redacted]

15.2 Investigator Signature Page

Protocol #: VX16-150-102	Version #: 5.0	Version Date: 25 May 2018
Study Title: A Phase 2, Randomized, Double-blind, Placebo-controlled, 6-Week, Parallel-design Study of the Efficacy and Safety of VX-150 in Treating Subjects With Pain Caused by Small Fiber Neuropathy		

I have read Protocol VX16-150-102, Version 5.0, 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