1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 2, Randomized, Double-blind, Active-controlled, Dose-ranging, Parallel-design Study of the Efficacy and Safety of VX-548 in Subjects With Painful Diabetic Peripheral Neuropathy

Vertex Study Number: VX21-548-103

[redacted]

Date of Protocol: 17 February 2023 (Version 3.0)

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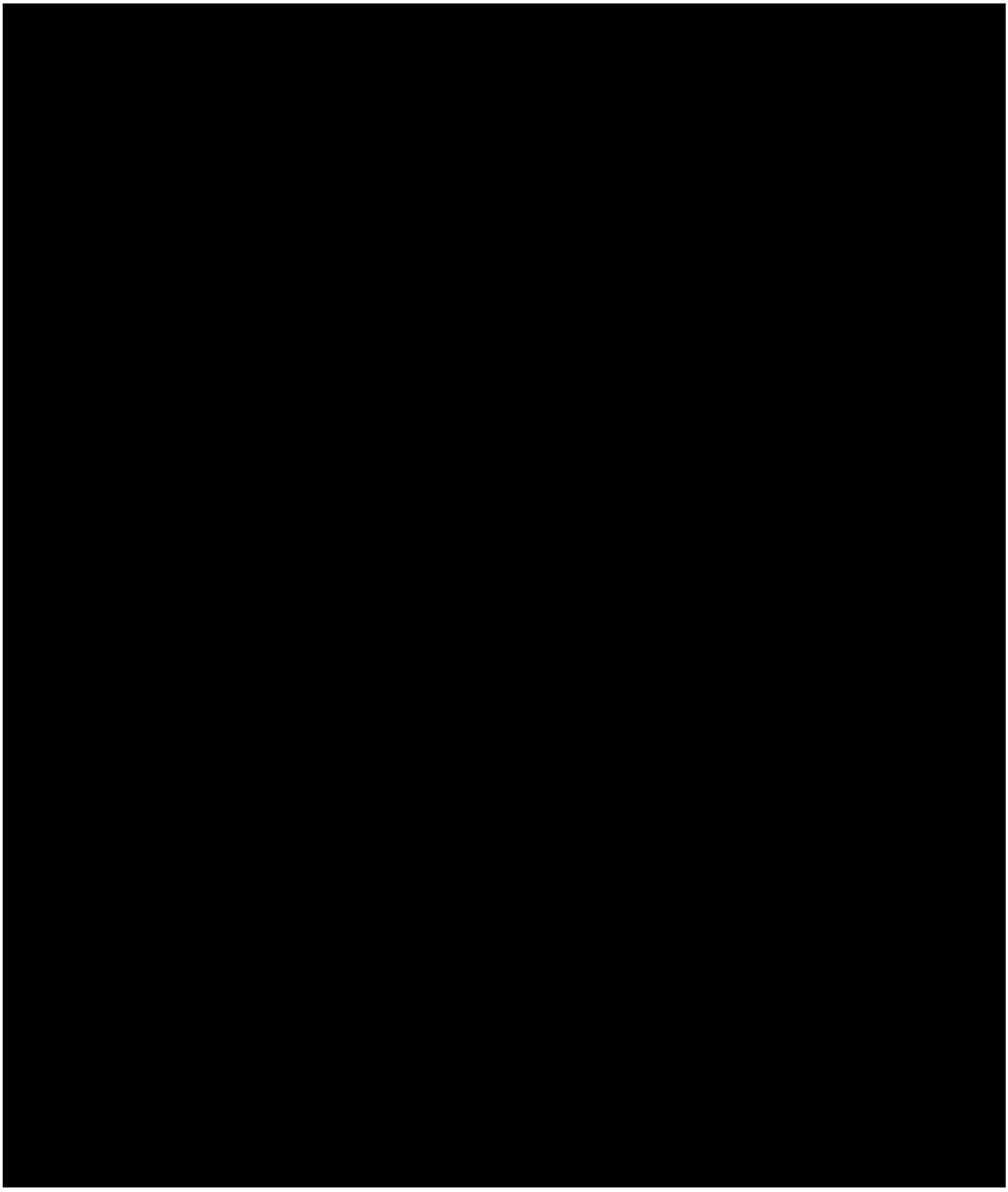


2 PROTOCOL SYNOPSIS

Title A Phase 2, Randomized, Double-blind, Active-controlled, Dose-ranging, Parallel-design Study of the Efficacy and Safety of VX-548 in Subjects With Painful Diabetic Peripheral Neuropathy

Brief Title Evaluation of Efficacy and Safety of VX-548 for Painful Diabetic Peripheral Neuropathy

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

Objectives

Primary Objectives

- To evaluate the efficacy of three VX-548 doses in treating subjects with painful diabetic peripheral neuropathy (DPN)
- To evaluate the safety and tolerability of VX-548

[redacted]

Endpoints

Primary Endpoint

- Change from baseline in the weekly average of daily pain intensity on a numeric pain rating scale (NPRS) at Week 12

Secondary Endpoints

- Change from baseline in the weekly average of the Daily Sleep Interference Scale (DSIS) at Week 12
- Proportions of subjects with ≥30%, ≥50%, and ≥70% reductions from baseline in the weekly average of daily pain intensity on the NPRS at Week 12
- Proportion of subjects categorized as much improved or very much improved at Week 12 on the patient global impression of change (PGIC) assessment
- Safety and tolerability based on the incidence and type of adverse events (AEs) and changes from baseline in clinically significant laboratory test results, vital signs, and ECGs at each visit

[redacted]

Number of Subjects Approximately 175 subjects

Study Population Male and female subjects 18 through 80 years of age, inclusive, with presence of bilateral pain in lower extremities due to DPN for at least 1 year, and weekly average NPRS pain score of ≥4 with limited variation in the Run-in Period

Investigational Drug Active substance: VX-548

Activity: $Na_V1.8$ inhibitor

Strength and route of administration: 23-mg tablets and matching placebo for oral administration

Reference Drug Active substance: Pregabalin

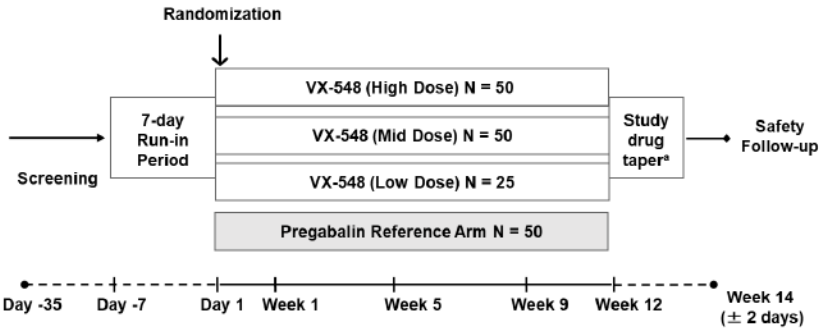
Activity: Calcium channel ($alpha_2$-delta site) inhibitor

Strength and route of administration: 100-mg capsules and matching placebo for oral administration

Study Duration Excluding the Screening Period (which includes a 7-day Run-in Period), each subject will participate in the study for approximately 14 weeks: a 12-week Treatment Period and a Safety Follow-up Visit 14 (± 2) days after the end of the Treatment Period.

Study Design This is a Phase 2, randomized, double-blind, active-controlled, dose-ranging, 4-arm, parallel-design study. Subjects who meet eligibility criteria during Screening Visits 1 and 2 will enter a 7-day Run-in Period to establish their baseline NPRS pain score. Subjects with a baseline average NPRS score of ≥4 points with limited variation (SD <25% of mean) will be eligible for the 12-week Treatment Period followed by a Safety Follow-up Visit (Figure 2-1).

Figure 2-1 VX21-548-103 Study Design



N: number of subjects

[a] At the end of the Treatment Period (Week 12), subjects will taper off capsule (pregabalin reference or matched placebo) study drug for 7 days.

A total of approximately 175 subjects will be randomized 2:2:1:2 to 4 treatment arms: VX-548 (high, mid, or low dose) or pregabalin (reference arm) (Table 2-1). Randomization will be stratified by sex (female and male) and body mass index (≥30 and <30 kg/m^2). To maintain the blind, all subjects will receive the same number of tablets once daily (qd) in the morning and the same number of capsules 3 times per day in a double-dummy design. After the Treatment Period, subjects will taper off capsule (pregabalin reference or matched placebo) study drug for 7 days (4 days of dosing every 12 hours, then 3 days of dosing qd), and the Safety Follow-up Visit will occur an additional 7 (± 2) days later.

Table 2-1 VX21-548-103 Treatment Arms

Treatment	Active Dose	Number of Subjects (Planned)
VX-548 (high dose)	69 mg qd	50
VX-548 (mid dose)	46 mg qd	50
VX-548 (low dose)	23 mg qd	25
Pregabalin	100 mg tid	50

qd: once daily; tid: 3 times per day
Note: To maintain the blind, all subjects will receive the same number of tablets and the same number of capsules at the same respective frequency (i.e., qd for tablets and tid for capsules during the Treatment Period) in a double-dummy design.

Subjects will stop taking pain medications (including pregabalin, if applicable), except acetaminophen (500 mg), for at least 14 days before the first dose of study drug.

Acetaminophen will be permitted as a pain rescue medication as needed (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. Subjects will record rescue medication use, and their current pain score on the NPRS immediately before each administration of rescue medication.

Assessments

Efficacy: 11-point NPRS, DSIS, PGIC, [redacted] use of rescue medication, and [redacted]

Safety: AEs; clinical laboratory assessments; clinical evaluation of vital signs, ECGs, and physical examination; and Columbia Suicide Severity Rating Scale

[redacted]

Statistical Analyses

The primary efficacy endpoint is the change from baseline in the weekly average of the daily pain intensity on an NPRS at Week 12. The primary analysis will be a within-group comparison in any VX-548 dose group.

The sample size is based on the primary analysis of the primary endpoint. With 37 evaluable subjects in the VX-548 high or mid dose group and 18 evaluable subjects in the VX-548 low dose group, there is more than 90% power in any VX-548 dose group to detect a mean change from baseline of 3 with a single group *t*-test at the 2-sided 0.05 significance level, assuming the SD is 2.3. With an evaluable sample size of 37, a 2-sided 95% CI for the mean change from baseline in the high or mid dose group will extend 0.77 on either side of the observed mean, assuming the CI is based on the *t*-statistic and the observed SD is 2.3. Under the same assumptions and an evaluable sample size of 18, a 2-sided 95% CI for the mean change from baseline in the low dose group will extend 1.14 on either side of the observed mean. To account for a 25% dropout rate, 50 subjects each will be enrolled in the VX-548 high dose, VX-548 mid dose, and the pregabalin groups; 25 subjects will be enrolled in the VX-548 low dose group. The total sample size is 175 subjects.

The primary efficacy analysis will be based on a mixed-effects model for repeated measures (MMRM), with change from baseline in weekly average of daily pain intensity score as the dependent variable; and fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline weekly average of daily pain intensity, and baseline weekly average of daily pain intensity-by-time interaction. The least squares (LS) mean change from baseline at Week 12 for each

group will be presented with the corresponding SE, and the corresponding 95% CI and *P* value.

3 SCHEDULE OF ASSESSMENTS

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

Table 3-1 Study VX21-548-103: Screening Period (Including 7-Day Run-in Period)

Event/Assessment[a]	Day -35 to Day -9 Screening Visit 1	Day -8 Screening Visit 2[b]	Day -7 to Day -1 Run-in Period	Comments
Informed consent	X			Must be obtained before performing any study-related procedures. Remote consent may be used if permitted by local regulations; Section 13.2.3.
Clinic or home health visit	X			Subjects will have the option to complete this visit in the clinic or to have a home health visit. Home health visits are only an option if permitted by local regulations. Section 9.1.1.1.
Telemedicine video conference or telephone contact	X			A consultation between the subject and investigator or qualified delegate (LIP) must be performed **within 2 business days after home health visit.** Required only for subjects who have a home health visit; not required for subjects who have a clinic visit; Section 9.1.5
Clinic visit		X		
Discontinue specified medications	X	X	X	Section 9.4
Demographics	X			
Medical history	X			
Weight, height, and BMI	X			Weight and height will be measured with shoes off.
Vital signs	X			Vital signs will be collected after the subject has been at rest (seated or supine) for at least 5 minutes; Section 11.5.3
Complete physical examination		X		At times other than Screening Visit 2, symptom-directed PEs may be performed at the discretion of the investigator or health care provider; Section 11.5.3
Standard 12-lead ECG		X		Standard 12-lead ECGs will be performed in triplicate after subjects have been at rest (supine) for at least 5 minutes; Section 11.5.4
Serum β-hCG	X			All biologically female subjects; Section 11.5.2
Serum FSH	X			Suspected postmenopausal female subjects only; Section 11.5.2
Serology (HBsAg, HCV Ab, and HIV-1/HIV-2 Abs)	X			Section 11.5.2
Serum chemistry	X			
Hematology	X			
Coagulation	X			
HbA1c	X			
Thyroid function test	X			
Vitamin B12	X			
Urinalysis	X			

Table 3-1 Study VX21-548-103: Screening Period (Including 7-Day Run-in Period)

Event/Assessment[a]	Day -35 to Day -9 Screening Visit 1	Day -8 Screening Visit 2[b]	Day -7 to Day -1 Run-in Period	Comments
Urine drug test	X	(X)		Subjects who have a positive screen for opioids (acute use only) or marijuana may repeat the test at Screening Visit 2, as noted by (X); the second test must be at least 7 days (marijuana) or at least 3 days (opioid) after the first. Section 11.5.2
Urine alcohol test	X			Section 11.5.2
Pain assessment training		X		Section 9.1.1.1
e-diary and ePRO training and device distribution		X		
NPRS via daily e-diary			X	Each morning, subjects will record their average daily NPRS score from the previous 24 hours. Subjects will also report their current pain score immediately before each administration of rescue medication, if applicable. Section 11.3.
DSIS via daily e-diary			X	Each morning, subjects will report on the previous night's sleep using the DSIS; Section 11.3.
Rescue medication use			X	Subjects will record NPRS pain score immediately before each administration and record date and time of administration in an e-diary; Section 11.3
Medication review	Continuous from signing of ICF through Safety Follow-up Visit			All medications taken within 14 days before Screening Visit 1 and selected prior medications taken earlier; Section 9.5
Treatment and procedures review	Continuous from signing of ICF through Safety Follow-up Visit			
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit			

β-hCG: beta-human chorionic gonadotropin; BMI: body mass index; DSIS: Daily Sleep Interference Scale; e-diary: electronic diary; ePRO: electronic patient-reported outcome; FSH: follicle-stimulating hormone; HbA1c: hemoglobin A1c (glycosylated hemoglobin); HBsAg: hepatitis B surface antigen; HCV Ab: hepatitis C virus antibody; HIV-1/HIV-2 Abs: antibodies against human immunodeficiency viruses 1 and 2; ICF: informed consent form; NPRS: numeric pain rating scale; PE: physical examination

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

[b] Screening Visit 2 may occur only after laboratory results from Screening Visit 1 are available and have established subject eligibility to continue study participation. Screening Visit 2 will be considered as Day -8.

Table 3-2 Study VX21-548-103: Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period							ETT Visit[c]	Taper[d]	Safety Follow-up Visit 14 (± 2) Days After End of Treatment Period	Comments
	Day 1[b]	Week 1 (± 1 Day)	Week 3 (± 3 Days)	Week 5 (± 3 Days)	Week 7 (± 3 Days)	Week 9 (± 3 Days)	Week 12 (± 3 Days)				
Clinic visit	X	X		X			X	X		X	
Clinic or home health visit			X		X	X					Subjects will have the option to complete these visits in the clinic or to have a home health visit. Home health visits are only an option if permitted by local regulations; Section 9.1.1
Telemedicine video conference or telephone contact			X		X	X					A consultation between the subject and investigator or qualified delegate (LIP) must be performed **within 2 business days after home health visit.** Required only for subjects who have a home health visit; not required for subjects who have a clinic visit; Section 9.1.5
Randomization	X										Occurs after eligibility is confirmed, including criteria for average NPRS during 7-day Run-in Period.
Weight	X	X		X			X	X			Weight will be measured with shoes off.
Vital signs	X	X	X	X	X	X	X	X			Vital signs will be collected after the subject has been at rest (seated or supine) for at least 5 minutes and before 12-lead ECG assessment or blood sampling. At the Day 1 and Week 5 visits, vital signs will be collected predose only; Section 11.5.3.
Standard 12-lead ECG	X	X		X			X	X			Standard 12-lead ECGs will be performed in triplicate after subjects have been at rest (supine) for at least 5 minutes; 12-lead ECGs will be done after taking vital signs and before any procedures that may affect

Table 3-2 Study VX21-548-103: Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period: Day 1[b]	Week 1 (± 1 Day)	Week 3 (± 3 Days)	Week 5 (± 3 Days)	Week 7 (± 3 Days)	Week 9 (± 3 Days)	Week 12 (± 3 Days)	ETT Visit[c]	Taper[d]	Safety Follow-up Visit 14 (± 2) Days After End of Treatment Period	Comments
											heart rate (e.g., blood sampling). At the Day 1 and Week 5 Visits, ECGs will be collected predose and at 2 and 4 hours postdose. At all other visits, ECGs will be collected during the visit without regard to dosing; Section 11.5.4.
Complete PE	X										Section 11.5.3
Abbreviated PE		As applicable									Symptom-directed PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator; Section 11.5.3.
BSTK evaluation	X						X	X			Section 11.4
NPRS via daily e-diary	Day 1 through Week 12										Each morning, before the first daily dose, subjects will record their average daily NPRS score from the previous 24 hours. Subjects will also report their current pain score immediately before each administration of rescue medication, if applicable. Section 11.3
DSIS via daily e-diary	Day 1 through Week 12										Each morning, before the first daily dose, subjects will report on the previous night's sleep using the DSIS. Section 11.3
PGIC		X		X			X	X		X	Section 11.3
[redacted]											
C-SSRS	X	X		X			X	X		X	Section 11.5.5
Urinalysis	X		X			X	X				Section 11.5.2
Drug and alcohol testing	X[e]		X			X	X	X			
Pregnancy test[f]	urine[e]	urine	urine	urine	urine	urine	serum	serum		urine	

Table 3-2 Study VX21-548-103: Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period: Day 1[b]	Week 1 (± 1 Day)	Week 3 (± 3 Days)	Week 5 (± 3 Days)	Week 7 (± 3 Days)	Week 9 (± 3 Days)	Week 12 (± 3 Days)	ETT Visit[c]	Taper[d]	Safety Follow-up Visit 14 (± 2) Days After End of Treatment Period	Comments
Coagulation							X	X			
Hematology	X		X			X	X	X			
Serum chemistry	X		X			X	X				
HbA1c							X	X			
[redacted]											
DNA blood sample (optional)	X										Optional DNA sample may be collected at any time on Day 1 after subject randomization (Section 11.4)
Nf-L biomarker sample	X	X		X			X	X			Section 11.4
Pain assessment training refresher				X							Section 9.1.1.1
Study drug administration	Day 1 through Week 12 (tablets qd in the morning and capsules tid). Day 1 and Week 5 first daily doses will be administered at the clinic. The last dose of tablet study drug will be on the morning of the Week 12 Visit. The tapering regimen for the capsule study drug will begin the following day.								X		Subjects will record the date and time of each dose administration in an e-diary. To maintain the blind, subjects will receive the same number of tablets and/or capsules at the same respective frequencies in each treatment group; Section 9.6
Study drug count		X	X	X	X	X	X	X		X	
Rescue medication use	Continuous from Day 1 through Week 12										Subjects will record NPRS pain score immediately before each administration and record date and time of administration in an e-diary; Section 11.3

Table 3-2 Study VX21-548-103: Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period: Day 1[b]	Week 1 (± 1 Day)	Week 3 (± 3 Days)	Week 5 (± 3 Days)	Week 7 (± 3 Days)	Week 9 (± 3 Days)	Week 12 (± 3 Days)	ETT Visit[c]	Taper[d]	Safety Follow-up Visit 14 (± 2) Days After End of Treatment Period	Comments
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										

[redacted]; BSTK: bedside sensory testing kit; C-SSRS: Columbia Suicide Severity Rating Scale; DSIS: Daily Sleep Interference Scale; e-diary: electronic diary; ETT: early termination of treatment; HbA1c: hemoglobin A1c (glycosylated hemoglobin); ICF: informed consent form; LIP: licensed independent practitioner; Nf-L: neurofilament light chain; NPRS: numeric pain rating scale; [redacted]; PE: physical examination; PGIC: patient global impression of change; [redacted]; q12h: every 12 hours; qd: once daily; [redacted] tid: 3 times per day

[a] At each visit, documentation of the previous day's NPRS score by the subject should be confirmed before performing any assessments. When assessment time points coincide, assessments will be performed in the following order: patient-reported outcomes (e.g., NPSI), vital signs, 12-lead ECG, PE, and blood sample collection.

[b] On Day 1 and the Week 5 visit, all assessments must be completed before the first daily dose of study drug, except for the postdose PK and ECG sampling.

[c] If a subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the subject decides to terminate study treatment; the subject will be encouraged to complete the capsule (pregabalin reference or matched placebo) study drug taper. Subjects who prematurely discontinue treatment will be encouraged to stay in the study, including completing the daily diaries and returning for clinical visits to complete study efficacy assessments (i.e., NPRS, PGIC, DSIS, NPSI, use of rescue medication, and SF-MPQ-2). These subjects will also be required to complete the Safety Follow-up Visit. If the ETT Visit occurs 14 days or later following the last tablet 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 ETT Visit is within a week of any scheduled visit in the Treatment Period, it will replace that scheduled visit, and a separate visit will not be required.

[d] After the Treatment Period (capsule dosing tid), subjects will taper off capsule (pregabalin reference or matched placebo) study drug as follows: 4 days of dosing q12h, then 3 days of dosing qd in the evening.

[e] Results from the Day 1 urine pregnancy, drug, and alcohol tests are required before the first dose.

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

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List of Abbreviations

Abbreviation	Definition
ADL	activities of daily living
AE	adverse event
AMSAP	abbreviated modeling and simulation analysis plan
ANCOVA	analysis of covariance
AUC_{0-24}	AUC from the time of dosing to 24 hours
β-hCG	beta-human chorionic gonadotropin
[redacted]	
BMI	body mass index
BSTK	bedside sensory testing kit
CD	compact disc
CI	confidence interval
[redacted]	
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DPN	diabetic peripheral neuropathy
DSIS	Daily Sleep Interference Scale
e-diary	electronic diary
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
ETT	Early Termination of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GPS	Global Patient Safety
H2	histamine type 2 receptor
HbA1c	hemoglobin A1c (glycosylated hemoglobin)
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
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IMP	investigational medicinal product

Abbreviation	Definition
IND	Investigational New Drug (application) (US)
IRB	institutional review board
IXRS	interactive response system in which X represents voice or web, such as IWRS
LIP	licensed independent practitioner
LS	least squares
max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum value
MMRM	mixed-effects model for repeated measures
n	size of subsample
Na_v	voltage-gated sodium channels
Nf-L	neurofilament light chain
NOAEL	no-observed-adverse-effect level
NPRS	numeric pain rating scale
[redacted]	
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamic
PE	physical examination
PGIC	patient global impression of change
PI	principal investigator
[redacted]	
prn	as needed
q12h	every 12 hours
qd	once daily
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]	
SNRI	selective norepinephrine reuptake inhibitor
SUSAR	suspected, unexpected, serious adverse reaction
TE	treatment emergent
tid	3 times per day
US	United States

Abbreviation of Study Numbers

Abbreviation	Study Number
Study 001	Study VX19-548-001
Study 002	Study VX20-548-002

5 INTRODUCTION

5.1 Background

Neuropathic pain may be defined as a process occurring after a primary lesion or disease of the somatosensory nervous system.[1] It is a major cause of disability worldwide, negatively affecting patient's sleep, mood, and functionality.[2] Antidepressants and anticonvulsants remain the first line treatment for neuropathic pain despite not being designed for such purpose.[3] Their use is often limited by an arsenal of side effects or inadequate pain relief. Pregabalin is an anticonvulsant approved for the treatment of painful diabetic neuropathy; it is considered first-line treatment in most international clinical guidelines and forms a key part of management of neuropathic pain.[4]

Clinical development has exhibited a considerable lack of recent progress and innovation of new medications to treat both acute and chronic pain. Over the last decades, most approved analgesic drugs for the treatment of neuropathic pain either act on the serotonin-norepinephrine system (such as the serotonin-norepinephrine reuptake inhibitor, duloxetine) or on voltage-gated calcium channels (such as the gabapentinoid, pregabalin).[5] Given the limited treatment options, combined with their risks and relative ineffectiveness, the development of analgesics targeting specific pathophysiology mechanisms with improved efficacy and safety profiles is vital for better pain management and patient health outcomes.

Voltage-gated sodium channel 1.8 ($Na_V1.8$) plays a critical role in pain signaling.[6, 7] Support for this assertion arises from (1) evaluation of the role $Na_V1.8$ plays in normal physiology[8-12], (2) pathological states arising from mutations in the $Na_V1.8$ gene (*SCN10A*)[13, 14], (3) animal models[15-18], and (4) pharmacology of known $Na_V1.8$-modulating agents.[19-21] In addition, because $Na_V1.8$ expression is restricted to peripheral neurons, particularly those that sense pain (e.g., the dorsal root ganglia)[8, 10], $Na_V1.8$ inhibitors are less likely to be associated with the side effects commonly observed with other sodium channel modulators and the abuse liability associated with opioid therapies. Therefore, targeting the underlying biology of pain through selective $Na_V1.8$ inhibition represents a novel approach to analgesic drug development that has the potential to address an urgent unmet need for safe and effective acute and chronic pain therapies.

VX-548 is being developed for the treatment of pain. VX-548 is a $Na_V1.8$ inhibitor that is highly selective for $Na_V1.8$ relative to other Na_V channels. Refer to the VX-548 Investigator's Brochure for additional details.[22]

5.2 Study Rationale

Clinical data from 2 Phase 1 studies evaluating single and multiple ascending doses of VX-548 demonstrated that VX-548 is generally safe and well tolerated in healthy subjects (Studies 001 and 002, respectively).[22]

This study will evaluate the efficacy and safety of three VX-548 doses in treating painful diabetic peripheral neuropathy (DPN).

6 STUDY OBJECTIVES

6.1 Primary Objectives

- To evaluate the efficacy of three VX-548 doses in treating subjects with painful DPN

- To evaluate the safety and tolerability of VX-548

[redacted]

7 STUDY ENDPOINTS

7.1 Primary Endpoint

- Change from baseline in the weekly average of daily pain intensity on a numeric pain rating scale (NPRS) at Week 12

7.2 Secondary Endpoints

- Change from baseline in the weekly average of the Daily Sleep Interference Scale (DSIS) at Week 12
- Proportions of subjects with ≥30%, ≥50%, and ≥70% reductions from baseline in the weekly average of daily pain intensity on the NPRS at Week 12
- Proportion of subjects categorized as much improved or very much improved at Week 12 on the patient global impression of change (PGIC) assessment
- Safety and tolerability based on the incidence and type of AEs and 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.

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) between the ages of 18 and 80 years, inclusive.
4. Body weight ≥45 kg and body mass index (BMI) of ≥18.0 to <40.0 kg/m^2.
5. Diagnosis of diabetes mellitus type 1 or type 2 with
    - glycosylated hemoglobin A1c (HbA1c) ≤9%;
    - in the opinion of the investigator, optimized glycemic control, and subject has been stable on oral hypoglycemics and/or subcutaneous insulin or dietary treatment for ≥3 months before Screening Visit 1; and
    - presence of bilateral pain in lower extremities due to DPN for at least 1 year.
6. Weekly average of daily NPRS ≥4 with limited variation in the 7-day Run-in Period (SD <25% of mean).

8.2 Exclusion Criteria

1. More than 3 missing daily NPRS scores during the 7-day Run-in Period.
2. Painful neuropathy other than DPN, such as post-herpetic neuralgia, post-traumatic nerve injury, diabetic amyotrophy, human immunodeficiency virus (HIV) neuropathy, immune sensory and autonomic polyneuropathy (e.g., Sjogren's syndrome), hereditary sensory and autonomic polyneuropathy, focal diabetic neuropathies (e.g., proximal motor neuropathy, mononeuropathy, mononeuropathy multiplex), or chronic regional pain syndrome.
3. History of any illness or any clinical condition that, in the opinion of the investigator or the subject's general practitioner, might confound the results of the study or pose an additional risk in administering study drug to the subject. This may include, but is not limited to, history of relevant drug or food allergies; history of significant respiratory, renal, hepatic, hematologic, cardiovascular, metabolic, neurologic, or psychiatric disease; history or presence of clinically significant pathology; and history of cancer, 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).
4. History of severe psychiatric disorder, suicidal ideation, and/or at risk of self-harm, harm to others, or suicide attempt.
5. History of cardiac dysrhythmias requiring anti-arrhythmia treatment(s) within the last 2 years; 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; history of QT prolongation or standard 12-lead ECG (performed in triplicate) demonstrating median QTcF >450 msec at Screening Visit 2; or clinical evidence of structural heart disease.
6. History of a clinical atherosclerotic event, such as myocardial infarction or stroke, within the past 12 months before Screening Visit 1

7. Impaired renal function defined as either creatinine clearance <60 mL/min or requiring hemodialysis.
8. History of significant hepatic disease, including but not limited to hepatic cirrhosis, portal hypertension, moderate or severe hepatic impairment (defined as Child-Pugh Class B or C).[23]
9. History of nonhealing skin ulcer disease that, in the opinion of the investigator or medical monitor, would preclude the subject's participation in the study.
10. Subjects with a history of severe retinopathy, defined as Stage 3 or greater. [24]
11. History of substance abuse 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. Alanine transaminase or aspartate transaminase values >2.5 × upper limit of normal.
13. Any other abnormal laboratory results indicative of significant medical disease that, in the opinion of the investigator, would preclude the subject's participation in the study.
14. A known or clinically suspected infection with HIV or hepatitis B or C viruses.
15. Subjects unwilling to receive any protocol-related medicine (e.g., acetaminophen, pregabalin).
16. Subjects with a history of allergy related to pregabalin and/or acetaminophen.
17. For biologically female subjects: Pregnant, nursing, or planning to become pregnant during the study or within 30 days after the last study drug dose.

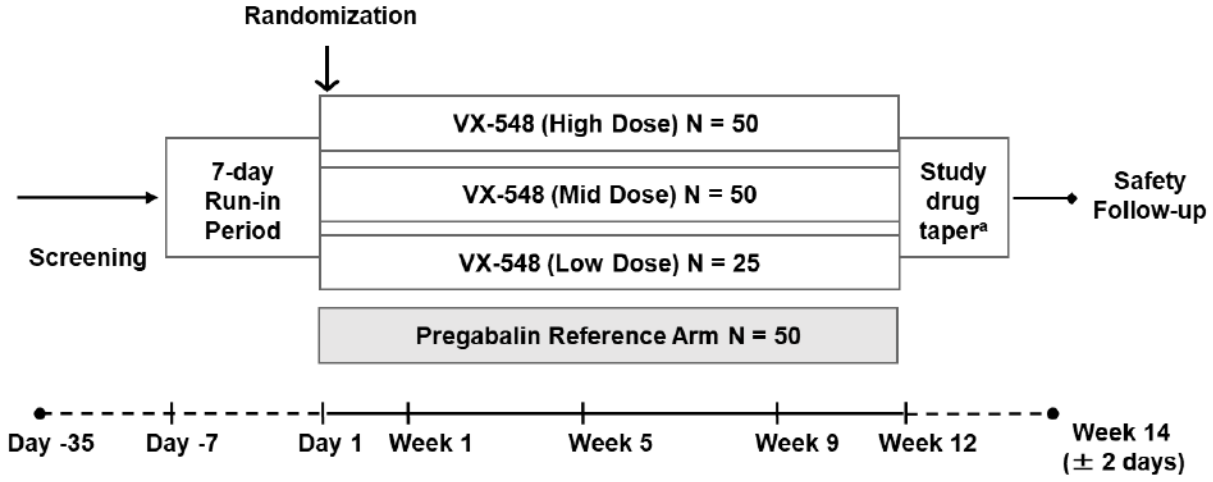
    For biologically male subjects: With a biologically female partner who is pregnant, nursing, or planning to become pregnant during the study or within 30 days after the last study drug dose.
18. Participation in a previous study investigating VX-548.
19. Participated in another investigational study within 30 days of the first dose of study drug.
20. Any treatment with opioids for chronic (including neuropathic) pain during the past 3 months or use of opioids for >7 days for an acute pain condition during the past 3 months before Screening Visit 1.
21. Evidence of misuse, aberrant use, or addiction to alcohol or an illicitly used drug of abuse in the past 3 years or a positive test for drugs of abuse as defined in Section 11.5.2.
    - A positive drug screen for a known prescribed concomitant medication that is not otherwise exclusionary (e.g., benzodiazepines) will not disqualify subjects.
22. Use of the substances, activities, or devices, as defined in Table 9-2, during the specified times.
23. 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, active-controlled, dose-ranging, 4-arm, parallel-design study. Subjects who meet eligibility criteria during Screening Visits 1 and 2 will enter a 7-day Run-in Period to establish their baseline NPRS pain score. Subjects with a baseline average NPRS score of ≥4 points with limited variation (SD <25% of mean) will be eligible for the 12-week Treatment Period followed by a Safety Follow-up Visit (Figure 9-1).

Figure 9-1 VX21-548-103 Study Design



N: number of subjects

[a] At the end of the Treatment Period (Week 12), subjects will taper off capsule (pregabalin reference or matched placebo) study drug for 7 days.

A total of approximately 175 subjects will be randomized 2:2:1:2 to 4 treatment arms: VX-548 (high, mid, or low dose) or pregabalin (reference arm; Table 9-1). Randomization will be stratified by sex (female and male) and BMI (≥30 and <30 kg/m^2). To maintain the blind, all subjects will receive the same number of tablets once daily (qd) in the morning and the same number of capsules 3 times per day (tid) in a double-dummy design. After the Treatment Period, subjects will taper off capsule (pregabalin reference or matched placebo) study drug for 7 days (4 days of dosing every 12 hours, then 3 days of dosing qd), and the Safety Follow-up Visit will occur an additional 7 (± 2) days later.

Subjects will stop taking pain medications (including pregabalin, if applicable), except acetaminophen (500 mg), for at least 14 days before the first dose of study drug.

Acetaminophen will be permitted as a pain rescue medication as needed (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. Subjects will record rescue medication use, and their current pain score on the NPRS immediately before each administration of rescue medication.

Table 9-1 VX21-548-103 Treatment Arms

Treatment	Active Dose	Number of Subjects
VX-548 (high dose)	69 mg qd	50
VX-548 (mid dose)	46 mg qd	50
VX-548 (low dose)	23 mg qd	25
Pregabalin	100 mg tid	50

qd: once daily; tid: 3 times per day

Note: To maintain the blind, all subjects will receive the same number of tablets and the same number of capsules at the same respective frequency (i.e., qd for tablets and tid for capsules during the Treatment Period) in a double-dummy design.

9.1.1 Screening

Screening assessments are listed in Table 3-1.

Screening will occur within 35 days before administration of study drug. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from each subject in person or remotely (Section 13.2.3) before performing any study-related procedure. If needed, Screening Visit 1 assessments may be performed on different days within the Screening Period (e.g., informed consent may be obtained before the home health visit, if applicable).

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 prn, following the guidelines in Section 9.4.1, as a rescue medication for intermittent pain.

9.1.1.1 Screening Visits 1 and 2

Screening Visit 1 can occur as early as Day -35 and may occur in the clinic or as a home health visit with a qualified visiting nurse if permitted by local regulations. Screening Visit 2 may occur only after laboratory results from Screening Visit 1 are available and have established subject eligibility to continue study participation per Section 8; Screening Visit 2 must occur at the clinic and will be considered as Day -8.

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. At Screening Visit 2, subjects will receive pain assessment trainings on accurate pain reporting, bias reduction, use of the electronic diary (e-diary) and electronic patient-reported outcome assessments. A refresher training on pain assessment will occur at the Week 5 Visit. Additional review of these educational materials may be repeated for some or all subjects depending on the findings of an ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level).

9.1.1.2 Run-in Period

The Run-in Period (Days -7 to -1) will begin the day following Screening Visit 2 (Day -8). During the Run-in Period, subjects will report their average daily pain from Day -7 to Day -1 as described in Section 11.3 to establish the baseline NPRS pain score. Pain treatment restrictions and use of acetaminophen as a rescue medication will continue to apply during the Run-in Period. Subjects will report their use of acetaminophen.

9.1.1.3 Repetition of Screening Assessment(s)

Repetition of any screening assessment that did not meet eligibility criteria is not permitted, unless specified in the protocol, or there is clear evidence of a laboratory error (e.g., hemolysis of sample). In all cases, the medical monitor must authorize retesting.

9.1.1.4 Rescreening and Screening Extensions

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

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

Screening Window Extensions

Any subject who is 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 42 days have elapsed from screening before first dose of study drug, all screening assessments need to be repeated.

9.1.2 Treatment Period

Treatment Period assessments are listed in Table 3-2.

All study periods will be conducted as described in Section 9.1. Dosing details are in Section 9.6. 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 selected assessments for all study visits, as described in Section 9.1.4.

9.1.3 Follow-up

After the Treatment Period, subjects will taper off capsule (pregabalin reference or matched placebo) study drug for 7 days as described in Section 9.1; tablet (VX-548 or matched placebo) study drug will not be provided during the taper. Subjects will have a Safety Follow-up Visit 14 (± 2) days after the end of the Treatment Period.

Safety Follow-up assessments are listed in Table 3-2.

9.1.4 Early Termination of Treatment

If a 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; the subject will be encouraged to complete the capsule (pregabalin reference or matched placebo) study drug taper.

Subjects who prematurely discontinue treatment will be encouraged to stay in the study, including completing the daily diaries and returning for clinical visits to complete study efficacy assessments (i.e., NPRS, PGIC, DSIS, [redacted] use of rescue medication, [redacted]). These subjects will also be required to complete the Safety Follow-up Visit, approximately 14 (± 2) days after their last tablet dose of study drug. The assessments performed at the Safety Follow-up Visit are listed in Table 3-2.

If the ETT Visit occurs 14 days or later following the last tablet 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 ETT Visit is within a week of any scheduled visit in the Treatment Period, it will replace that scheduled visit, and a separate visit will not be required.

If a subject withdraws consent for the study, no further assessments will be performed. Vertex may retain and continue using the study data and samples after the study ends, and may use the samples and information in the development of the study compound, for other drugs and diagnostics, in publications and presentations, and for educational purposes. If a subject withdraws from the study, the study data and samples collected will remain part of the study (Section 9.10).

9.1.5 Home Health Visits

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

9.2 Method of Assigning Subjects to Treatment Groups

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

9.3 Rationale for Study Elements

9.3.1 Study Design

This study is designed to evaluate the efficacy of VX-548 for treatment of pain in subjects with painful DPN. The randomized, double-blind study design will limit observer bias and reduce the possibility for unblinding. For the primary endpoint, daily NPRS 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

VX-548 doses (Table 9-1) were selected based on favorable safety and PK data from healthy volunteers in Study 001 (single ascending dose study) and Study 002 (multiple ascending dose study). Multiple oral doses up to 65 mg administered in solution/suspension under fasted conditions every 24 hours for 14 days have been evaluated and found to be safe and well tolerated.[22] The selected VX-548 doses are predicted to achieve concentrations that are able to produce 80% (low dose) to 90% (high dose) $Na_V1.8$ inhibition in the in vitro human dorsal root ganglia assay.

Based on observed data, the mean exposures (AUC_{0-24} and C_{max}) for VX-548 and its major metabolite, M6-548, at the highest dose in this study (69 mg qd without regard to food administered as tablets) are predicted to provide the following safety margins to the no-observed-adverse-effect level (NOAEL) observed in monkey in the 13-week GLP toxicity study:[22]

- VX-548: 2.8-fold and 4.5-fold below the NOAEL for AUC_{0-24} and C_{max}, respectively
- M6-548: 2.8-fold and 5.9-fold below the NOAEL for AUC_{0-24} and C_{max}, respectively

The safety margins were calculated using observed PK data for the suspension/solution formulation of VX-548 and adjusted based on the relative bioavailability between the tablet and solution formulations of VX-548 and relative bioavailability between fasted conditions and fed conditions with high-fat meal for the tablet formulation.

9.3.3 Rationale for Study Assessments

11-point NPRS: Pain intensity is the FDA-recommended efficacy endpoint for studies of pain drugs.[25, 26] 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).

DSIS: Pain frequently interferes with sleep, and sleep is important to quality of life. The FDA recommends evaluating the effect of analgesics on sleep.[25, 26] DSIS is commonly used in neuropathic pain studies and is assessed on an 11-point numeric rating scale. The 11-point scale ranges from 0 (none) to 10 (severe).

PGIC: The PGIC is commonly used in neuropathic pain studies, and the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group recommends it as a core outcome measure for chronic pain studies.[26] 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.[27] The assessment consists of a single item on a 7-point scale from 1 (very much improved) to 7 (very much worse).

[redacted]

Use of rescue medications: Data on the use of rescue medications are collected for descriptive analysis.

[redacted]

[redacted]

Columbia Suicide Severity Rating Scale (C-SSRS): The FDA recommends the evaluation of suicidality in clinical studies involving drugs with CNS activity. The C-SSRS evaluates this through a series of questions about suicidal thoughts and behaviors.

[redacted]

Bedside Sensory Testing Kit (BSTK): The BSTK is used for the purpose of standardized assessment and phenotyping of subjects' pain, using the usual components of a neurosensory examination.

9.4 Study Restrictions

Study restrictions are summarized in Table 9-2. A non-exhaustive list of study restrictions will be provided in the Study Reference Manual.

Table 9-2 Study Restrictions

Restricted Medication/Food/Activity [a]	Timing of Restriction	
	Start	**Stop**
Other investigational drugs or devices	30 days before first dose of study drug, 5 half-lives before first dose of study drug, or time determined by local requirements (whichever is longer)	Completion of SFU assessments
Any opioid use for chronic (including neuropathic) pain; for acute use, refer to Section 8.2 and Section 11.5.2	3 months before Screening Visit 1	Completion of Week 12 or ETT Visit assessments
Marijuana or marijuana products	14 days before first dose of study drug	Completion of Week 12 or ETT Visit assessments
Pregabalin (except use of reference study drug) and gabapentin	14 days before first dose of study drug	Completion of study drug taper (i.e., 7 days after Week 12 or ETT Visit)
Capsaicin patch	90 days before first dose of study drug	Completion of Week 12 or ETT Visit assessments
Lamotrigine, carbamazepine, oxcarbazepine, phenytoin, topiramate, valproic acid, mexiletine, and topical agents being prescribed for pain control	14 days before first dose of study drug	Completion of Week 12 or ETT Visit assessments

Table 9-2 Study Restrictions

Restricted Medication/Food/Activity [a]	Timing of Restriction	
	Start	Stop
All SNRIs and tricyclic antidepressants	14 days before first dose of study drug	Completion of Week 12 or ETT Visit assessments
All other treatments for pain, except acetaminophen (500 mg) and study drug (as outlined in Section 9.4.1), including nonpharmaceutical interventions	14 days before first dose of study drug	Completion of Week 12 or ETT Visit assessments
Oral steroids	5 half-lives or 2 days (whichever is longer) before first dose of study drug	Until last dose of study drug is taken
Medications, herbal and dietary supplements (including St. John's wort) known to be moderate or strong inducers of CYP3A	14 days before first dose of study drug	Completion of SFU assessments
Proton Pump Inhibitors	72 hours before first dose of study drug	Until last dose of study drug is taken
H2 blockers	12 hours before each morning dose of study drug	6 hours after each morning dose of study drug
Antacids	2 hours before each dose of study drug	2 hours after each dose of study drug
Grapefruit or grapefruit juice, pomelos, star fruit, Seville oranges and their juices, vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats	7 days before first dose of study drug	Completion of SFU assessments

ETT: Early Termination of Treatment; H2: histamine type 2 receptor; SFU: Safety Follow-up; SNRI: selective norepinephrine reuptake inhibitor

[a] Refer to the Study Reference Manual for a more complete list of medications prohibited/restricted in the study. See Section 9.5 for guidance on concomitant medications.

9.4.1 Treatments for Pain

- Subjects will abstain from all treatment for pain (including medications, supplements, and non-pharmaceutical therapies) starting from 14 days before the first dose of study drug, or as indicated in Table 9-2, and continuing through the time periods indicated in Table 9-2. For treatments that require a taper prior to discontinuation, the appropriate taper should be completed by 14 days before the first dose of study drug. Subjects taking aspirin for cardiovascular health may remain on their stable dose throughout the study.
- Subjects are not required to stop taking acetaminophen (500 mg) during the 14-day period before the first dose of study drug. 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. Subjects will record rescue medication use, and their current pain score on the NPRS immediately before each administration of rescue medication.

9.5 Prior and Concomitant Medications

- Subjects will abstain from all concomitant medications as described in the exclusion criteria (Section 8.2) and study restrictions (Table 9-2).
- All medications taken for the treatment of pain within 12 months of Screening Visit 1 will be recorded with indication, route of administration, and start and stop dates of administration; for any discontinued medications, the reason for discontinuation will also be recorded.
- All opioid medications taken within 12 months of Screening Visit 1 will be recorded with indication, route of administration, and start and stop dates of administration.
- All medications taken from 14 days before Screening Visit 1 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.

9.6 Administration

Study drug will be administered according to the following guidelines:

- Subjects will record the date and time of each dose administration in an e-diary.
- To maintain the blind, all subjects will receive the same number of tablets and/or capsules in a double-dummy design as summarized below and in Table 9-3:
    - VX-548 active or VX-548 placebo (as 3 tablets) will be administered to all subjects qd in the morning (with the first daily dose of pregabalin active or placebo capsule).
    - Pregabalin active or pregabalin placebo (as 1 capsule) will be administered to all subjects tid approximately 6 to 8 hours apart (i.e., 3 times during waking hours daily).

Table 9-3 Daily Study Drug Tablet and Capsule Administration by Treatment Group

	Number of Tablets		Number of Capsules[a]	
Treatment Arm	**VX-548 Active**	**VX-548 Placebo**	**Pregabalin Active**	**Pregabalin Placebo**
VX-548 (high dose)	3	0	0	3
VX-548 (mid dose)	2	1	0	3
VX-548 (low dose)	1	2	0	3
Pregabalin	0	3	3	0

tid: three times per day

[a] Pregabalin capsules (active or placebo) will be administered tid approximately 6 to 8 hours apart.

- Subjects will take study drug at approximately the same time each day and will administer orally with approximately 240 mL (8 fluid ounces) of water. Study drug may be taken with or without food.
- Subjects will swallow the study drug whole and will not chew it before swallowing.
- The Day 1 and Week 5 first daily doses will be administered at the clinic, and both predose and postdose PK samples, and predose and postdose 12-lead ECGs, will be collected; therefore, these 2 visits should be scheduled to start in the morning, and the subject should not take the morning dose (tablets and capsule) at home. On all other days (including visit days, regardless of scheduled visit time) the morning dose will be taken at home.

Missed Doses

- If a subject forgets the morning dose (tablets and capsule) and remembers within 2 hours of the scheduled dose, they will take the dose at that time and resume their normal schedule for the following doses.
- If a subject forgets the morning dose (tablets and capsule), and more than 2 hours have elapsed, they are to skip that capsule dose and resume at the next scheduled dose, but should take the tablets with the midday capsule dose. If a subject continues to forget the tablet dose and more than 2 hours have passed since the scheduled midday capsule dose, the subject should skip that tablet dose and resume at the next scheduled tablet dose (i.e., the next day).
- A capsule should not be taken within 4 hours of the last capsule, and 2 capsules should not be taken together. Therefore, assuming a schedule of every 6 hours during waking hours, if a subject forgets the midday dose (capsule), and more than 2 hours have elapsed, they are to skip that capsule dose and resume at the next scheduled dose.

Last Dose

The last dose of tablet study drug will be taken on the morning of the Week 12 Visit according to the subject's daily schedule, along with the morning dose of capsule study drug for that day. The midday and evening doses of capsule study drug will be taken as usual that day.

Taper

The taper regimen for the capsule study drug will begin the day after the Week 12 Visit. Dosing for this 7-day taper is as follows: 1 capsule in the morning and 1 capsule in the evening for 4 days, followed by 1 capsule in the evening for 3 days; the taper is then complete.

9.7 Dose Modification for Toxicity

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

9.8 Individual Stopping Rules and Precautions

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

- a serious adverse event (SAE) of heart failure that is considered related or possibly related to VX-548 by the investigator or Vertex; or
- an SAE of ventricular arrhythmia that is considered related or possibly related to VX-548 by the investigator or Vertex.

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

9.9 General Study Drug Interruption and Stopping Rules

Enrollment and dosing will be paused if any of the following events occur and are considered related or possibly related to VX-548 by the investigator or Vertex:

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

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

9.10 Removal of Subjects

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

Subjects who discontinue study treatment early will be encouraged to complete the taper and to continue to return for study efficacy assessments; additional details are provided in Section 9.1.4.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit, if applicable (see Section 9.1.4) and follow up with the subject regarding any unresolved AEs.

If a subject withdraws consent for the study, no further assessments will be performed. Vertex may retain and continue using the study data and samples after the study ends, and may use the samples and information in the development of the study compound, for other drugs and diagnostics, in publications and presentations, and for education purposes. If a subject withdraws from the study, the study data and samples collected will remain part of the study. A subject will not be able to request the withdrawal of his/her information from the study data. A subject may request destruction of the samples collected from him/her during the study as long as those samples can be identified as his/her samples.

9.11 Replacement of Subjects

Subjects who withdraw or are withdrawn during the study drug treatment period will not be replaced.

10 STUDY DRUG INFORMATION AND MANAGEMENT

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 23-mg VX-548 tablets, 100-mg pregabalin capsules, and matching placebos (tablets and capsules). Study drug labeling will be in compliance with applicable local

and national regulations. Additional details about packaging, labeling, and dispensing for VX-548 will be in the Pharmacy Manual.

10.3 Study Drug Supply, Storage, and Handling

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

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

Table 10-1 Study Drug

Drug Name	Dosing Form/ Route	Dosage	How Supplied
VX-548	Tablet/oral	23, 46, or 69 mg qd	Supplied as 23-mg tablets
VX-548 placebo	Tablet/oral	0 mg qd	Supplied as tablets
Pregabalin	Capsule/oral	100 mg tid	Supplied as 100-mg capsules
Pregabalin placebo	Capsule/oral	0 mg tid	Supplied as capsules

qd: once daily; tid: 3 times per day

10.4 Drug Accountability

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

10.5 Disposal, Return, or Retention of Unused Drug

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

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

10.6 Compliance

To ensure treatment compliance, the investigator or designee will supervise all study drug dosing that occurs at the site. At each visit, site personnel or approved home nurse will review that the

subject is compliant with study drug dosing and remind the subject of study drug dosing requirements. Compliance will also be assessed by ongoing study drug count in the clinic or checked by home nurse during home visits.

If a subject demonstrates continued noncompliance of study drug dosing despite educational efforts, the investigator will contact the medical monitor to discuss discontinuing the subject from the study.

10.7 Blinding and Unblinding

This is a double-blind study.

10.7.1 Blinding

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

- Any site personnel for whom this information is important to ensure the safety of a subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of a subject and a fetus in the event of a pregnancy
- Vertex GPS and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations
- External vendor (unblinded) statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IXRS Management for IXRS oversight and system administration
- Vertex Clinical Supply Chain
- The bioanalytical contract research organization (CRO) laboratory/vendor personnel managed by Vertex Bioanalysis
- The Vertex bioanalytical personnel responsible for reviewing raw data from the bioanalytical CRO, who is not a member of the SET (the Vertex bioanalytical SET member will continue to be blinded)

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

A limited Vertex team not directly involved in the conduct of the study may be unblinded to individual subject treatment assignments and have access to PK, efficacy, and/or safety data (e.g., AEs, clinical laboratory assessments) for continuous monitoring purposes. These individuals will not be members of the study team and will not interact with the study personnel. No unblinded data or results of unblinded analyses will be shared with blinded Vertex personnel. Masked identifications will be used for PK analyses. All instances of unblinding by Vertex personnel will be documented.

10.7.2 Unblinding

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

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

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

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor will be notified within 24 hours of the unblinding event. The reason and the date of the unblinding will be documented clearly in the subject's study file. Information about the treatment assignment obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with Vertex, the CRO, or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS or designee, per Section 13.1.2.

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

11 ASSESSMENTS

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

11.1 Subject and Disease Characteristics

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

[redacted]

11.2.3 Bioanalysis

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

11.3 Efficacy

11-point NPRS: Pain intensity will be evaluated using the 11-point NPRS. From Day -7 through Week 12, subjects will report their average daily pain during the last 24 hours on the NPRS via e-diary; during the treatment period, the NPRS should be completed in the morning before the first daily dose. Subjects will also report their current pain score before each administration of rescue medication. The NPRS scores from the daily e-diary will be used in the primary endpoint analysis, and the proportion of subjects with ≥30%, ≥50%, and ≥70% reduction from baseline in weekly average scores as reported in the daily e-diary will be used in the secondary endpoint analyses.

DSIS: The DSIS will be completed each morning before the first daily dose (and during the run-in period) in an e-diary to describe how pain interfered with the subject's sleep.

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

[redacted]

Use of rescue medications: Subjects will record rescue medication use, and their pain on the NPRS immediately before each administration of rescue medication in an e-diary.

[redacted]

Access to NPRS and DSIS Scores

Individual NPRS and DSIS scores will not be disclosed to the study sites.

Subjects should not have access to their previous study-related NPRS and DSIS scores until Vertex has determined that the study has completed (i.e., clinical study report [CSR] finalization), regardless of whether the subject permanently discontinues treatment.

11.5 Safety

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

11.5.1 Adverse Events

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

11.5.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory, unless otherwise specified. On Day 1, blood samples will be collected before the first dose of the study drug. At all other scheduled visits, these samples will be collected at any time during the visit.

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

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

Table 11-2 Safety Laboratory Test Panels

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

[a] If urinalysis results are positive for protein or blood, microscopic examination of urine will be performed and results provided for leukocytes, erythrocytes, crystals, bacteria, and casts.
[b] If blood urea nitrogen cannot be collected, urea may be substituted.

Clinical laboratory assessments from Screening Visit 1 must have no clinically significant findings that preclude participation in the study, as judged by the investigator, for a subject to proceed to Screening Visit 2 and to receive study drug on Day 1.

Additional tests at screening: The following additional tests will be performed during screening (at Screening Visit 1) to assess eligibility:

- Serum β-human chorionic gonadotropin (β-hCG) test for all biologically female subjects
- Serum follicle-stimulating hormone (FSH) for female subjects who are suspected to be postmenopausal; for a subject to be considered of nonchildbearing potential, the serum FSH levels will be within the laboratory's range for postmenopausal females
- Serology will include testing for hepatitis B surface antigen, hepatitis C virus antibody, and antibodies against HIV-1/HIV-2. Confirmatory HIV-1/2 Ab differentiation and HIV-1 RNA Qualitative TMA will be performed for positive antibodies against HIV-1/HIV-2. Confirmatory Hep C RNA PCR will be performed for positive hepatitis C virus antibody.
- HbA1c
- Thyroid function test
- Vitamin B12
- Drug and alcohol testing

Drug and alcohol testing: Opioids, methadone, cannabinoids, cocaine, amphetamines/ methamphetamines, barbiturates, and benzodiazepines will be assessed by a urine test at Screening Visit 1 and on Day 1. Alcohol will be assessed by a urine test at Screening Visit 1 and by a urine, blood, or breath test on Day 1 and thereafter. During treatment, drug and alcohol testing will be performed per Table 3-2. Subjects may also undergo random urine drug screening and alcohol testing if deemed appropriate by the investigator.

Drug and alcohol test results must be negative for subjects to receive study drug. However, subjects who have a positive screen for opioids (acute use only) or marijuana at Screening Visit 1 may repeat the test at Screening Visit 2; the second test must be at least 7 days (marijuana) or at least 3 days (opioid) after the first. A positive drug screen for a known prescribed concomitant medication that is not otherwise exclusionary (e.g., benzodiazepines) will not disqualify subjects.

Pregnancy testing for female subjects of childbearing potential (as defined in Section 11.5.6.1):

All biologically female subjects will have a serum pregnancy test at Screening Visit 1. Subsequent pregnancy tests will be performed only for female subjects of childbearing potential (as defined in Section 11.5.6.1) as follows:

- A serum pregnancy test will be performed at the Week 12 or ETT Visit.
- Urine pregnancy tests will be performed at all other visits that require pregnancy testing. At Weeks 3, 7, and 9, the urine pregnancy test may be done either at home or at the study site.

Both the screening (serum) and Day 1 (urine) pregnancy (β-hCG) tests must be negative for a subject to receive study drug. During treatment, if a urine pregnancy test is positive, all study drug dosing will stop, and the pregnancy will be confirmed with a serum β-hCG test. If pregnancy is confirmed, the procedures outlined in Section 11.5.6.2 will be followed.

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

Only laboratory tests done in the central laboratory may be used for the safety panels (Table 11-2), the serum pregnancy tests, and the Screening Visit 1 urine drug and alcohol tests; local laboratories and in-clinic (or in-home, where indicated) testing may be used for drug and alcohol tests after Screening Visit 1 and for all urine β-hCG pregnancy tests. In addition, local laboratories may be used at the discretion of the local investigator for management of urgent medical issues. If a local laboratory test value is found to be abnormal and clinically significant, it will be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. If it is not possible to send a timely specimen to the central laboratory (e.g., the subject was hospitalized elsewhere), the investigator may base the assessment of an AE on the local laboratory value.

11.5.3 Physical Examinations and Vital Signs

A PE of all body systems will be performed at Screening Visit 2 and Day 1. At other visits, symptom-directed PEs can be performed at the discretion of the investigator or healthcare provider. Vital signs assessments will be performed at Screening Visit 1 and at each clinic or home health visit.

A PE includes a review of the following systems: head, neck, and thyroid; eyes, ears, nose, and throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically

indicated. After screening, any clinically significant abnormal findings in a PE will be reported as AEs. If there is a PE finding during a home visit, depending on its severity and at investigator discretion, the subject may be instructed to have a PE or other evaluation in the clinic.

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

11.5.4 Electrocardiograms

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

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

The acceptable window for the 2- and 4-hour postdose ECGs on Day 1 and Week 5 is ± 30 minutes relative to the scheduled nominal time.

A printout of the ECG traces will be made for safety review by the investigator and maintained with source documentation. Clinically significant ECG abnormalities occurring during the study through the Safety Follow-up Visit will be recorded as AEs.

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

11.5.5 Columbia Suicide Severity Rating Scale

The C-SSRS will be performed as outlined in Table 3-2.

11.5.6 Contraception and Pregnancy

11.5.6.1 Contraception

Study participation requires compliance with the contraception guidelines outlined below.

Contraception for the couple is waived for the following:

- True abstinence for the subject. The subject must confirm that they will practice true abstinence from Screening Visit 1 through 30 days after the last dose of study drug. True abstinence is important to differentiate from periodic abstinence (e.g., calendar, ovulation,

symptothermal, postovulation methods) and withdrawal, which are not acceptable methods of contraception.

- If the male is infertile (e.g., bilateral orchiectomy). Infertility may be documented through examination of a semen specimen.
- If the female is of non-childbearing potential. To be considered of non-childbearing potential, the female must meet at least 1 of the following criteria:
    - Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum FSH level within the laboratory's reference range for postmenopausal females
    - Documented bilateral oophorectomy and/or hysterectomy
- Same biological sex relationships.

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

Table 11-3 Acceptable Methods of Contraception

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

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

Additional notes:

- If over the course of the study the subject meets the criteria for waiving the contraception requirements, the subject does not need to follow the contraceptive methods listed in Table 11-3.
- Male subjects must not donate sperm from the first study drug dose, throughout the study, and for 90 days following the last dose of study drug.
- Male and female subjects who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active.

- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.

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

11.5.6.2 Pregnancy

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

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

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

12 STATISTICAL ANALYSIS

This section presents a summary of the principal features of the planned statistical analyses. 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 clinical database lock.

12.1 Sample Size and Power

The primary efficacy endpoint is the change from baseline in the weekly average of the daily pain intensity on an NPRS at Week 12. The primary analysis will be a within-group comparison (i.e., change from baseline) in any VX-548 dose group.

The sample size is based on the primary analysis of the primary endpoint. With 37 evaluable subjects in the VX-548 high or mid dose group and 18 evaluable subjects in the VX-548 low dose group, there is more than 90% power in any VX-548 dose group to detect a mean change from baseline of 3 with a single group *t*-test at the 2-sided 0.05 significance level, assuming the SD is 2.3. With an evaluable sample size of 37, a 2-sided 95% CI for the mean change from baseline in the high or mid dose group will extend 0.77 on either side of the observed mean, assuming the CI is based on the *t*-statistic and the observed SD is 2.3. Under the same assumptions and an evaluable sample size of 18, a 2-sided 95% CI for the mean change from baseline in the low dose group will extend 1.14 on either side of the observed mean. To account for a 25% dropout rate, 50 subjects each will be enrolled in the VX-548 high dose, VX-548 mid dose, and the pregabalin groups; 25 subjects will be enrolled in the VX-548 low dose group. The total sample size is approximately 175 subjects.

The study is not powered for comparison between the VX-548 doses and the pregabalin reference arm.

12.2 Analysis Sets

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

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 to summarize subject demographics and baseline characteristics, and for all efficacy analyses, unless otherwise specified. Subjects will be analyzed according to the treatment to which they were randomized.

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, unless otherwise specified.

[redacted]

12.3 Statistical Analysis

12.3.1 General Considerations

All individual subject data for subjects who were randomized or received at least 1 dose of study drug will be presented in individual subject data listings.

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

Categorical variables will be summarized using counts and percentages.

Baseline values for the NPRS daily pain intensity scores and DSIS will be defined as the average score from Day -7 to Day -1. For ECGs, the baseline value will be defined as the average of the non-missing pretreatment measurements (triplicate) on Day 1. For all other variables, baseline values will be defined as the most recent non-missing measurement collected before the first dose of study drug.

Change (absolute change) from baseline will be calculated as post-baseline value – baseline value.

Treatment-emergent (TE) period will include the time period starting from the date of the first dose of study drug to either (1) the Safety Follow-up Visit, (2) the ETT Visit if it replaces the Safety Follow-up Visit, or (3) 14 days after the last dose date for subjects who do not have a Safety Follow-up Visit or equivalent. The TE Period will be used for safety analyses unless specified otherwise.

12.3.2 Background Characteristics

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, exposure, compliance, and important protocol deviations will be summarized.

12.3.3 Efficacy Analysis

All efficacy endpoints will be analyzed based on the FAS. Only the principal features of the efficacy analysis will be presented in this section. Details of all analyses will be provided in the SAP.

12.3.3.1 Analysis of Primary Endpoint

The primary efficacy endpoint is the change from baseline in the weekly average of the daily pain intensity on an NPRS at Week 12. The primary analysis will be a within-group comparison in any VX-548 dose group.

The primary efficacy analysis will be based on a mixed-effects model for repeated measures (MMRM), with change from baseline in weekly average of daily pain intensity score as the dependent variable; and fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline weekly average of daily pain intensity, baseline weekly average of daily pain intensity-by-time interaction. The least squares (LS) mean change from baseline at Week 12 for each group will be presented with the corresponding SE and the corresponding 95% CI and *P* value.

12.3.3.2 Analysis of Secondary Efficacy Endpoints

The proportion of subjects with ≥30% reduction from baseline in the weekly average of daily pain intensity on the NPRS at Week 12 will be summarized descriptively by treatment group and analyzed using the Cochran-Mantel-Haenszel test (stratified by sex and BMI). The proportion of subjects with ≥50% and ≥70% reduction from baseline will be analyzed similarly.

The proportion of subjects categorized as much improved or very much improved at Week 12 on the PGIC assessment will be summarized descriptively by treatment group and analyzed using the Cochran-Mantel-Haenszel test (stratified by sex and BMI).

The change from baseline in the weekly average of the DSIS at Week 12 will be analyzed similarly to the primary endpoint.

12.3.3.3 Multiplicity Adjustment

There is no multiplicity adjustment for this Phase 2 study.

[redacted]

12.3.4 Safety Analysis

The overall safety profile of VX-548 will be assessed in terms of the following safety and tolerability endpoints:

- Incidence of treatment-emergent AEs
- Clinical laboratory values
- Standard 12-lead ECG outcomes
- Vital signs
- C-SSRS

Safety endpoints will be analyzed based on the Safety Set. No statistical testing will be conducted. All safety data will be presented in individual subject data listings. Additional details will be provided in the SAP.

12.4 Interim Analysis

Not applicable.

12.5 Data Monitoring Committee Analysis

Not applicable.

12.6 Clinical Pharmacology Analysis

[redacted]

12.6.2 [redacted]/Pharmacodynamic Analysis

A population [redacted] analysis of plasma concentration versus time data of VX-548 and M6-548 may be performed using the nonlinear mixed-effects modeling approach. A population approach may also be used to investigate the exposure-response relationship for the efficacy and safety variables. A more detailed description of the methodology to be followed will be presented in the modeling and simulation analysis plan (MSAP). The results of the population [redacted] and [redacted]/pharmacodynamic (PD) analysis (if done) will be reported in a separate document.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

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

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

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

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

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

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

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time the ICF is signed until the following times:

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, the earliest of
    - 14 days after the last dose of tablet study drug, or
    - the ETT Visit, if that visit is 14 days or later following the last dose of tablet study drug (see Section 9.1.4).

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

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

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed May 2022). The severity of an AE described by a term that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

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

Source: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed May 2022)
ADL: activities of daily living; AE: adverse event
Note: A semi-colon indicates 'or' within the description of the grade.
[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

13.1.1.5 Adverse Event Causality

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

Table 13-2 Classifications for AE Causality

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

AE: adverse event

13.1.1.6 Study Drug Action Taken

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

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

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

AE: adverse event

[a] Refer to Section 9.7 for directions regarding what drug actions are permitted per protocol.

13.1.1.7 Adverse Event Outcome

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

Table 13-4 Classifications for Outcome of an AE

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

AE: adverse event

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

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

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

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

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

13.1.2.2 Reporting and Documentation of Serious Adverse Events

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

For SAEs that occur after obtaining informed consent and assent (where applicable) through the Safety Follow-up Visit, the SAE Form will be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report

follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

Email: globalpatientsafety@vrtx.com (preferred choice)

Fax: +1-617-341-6159

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

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

13.1.2.3 Expedited Reporting and Investigator Safety Letters

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

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

13.2 Administrative Requirements

13.2.1 Product Complaints

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

Product complaints are to be reported to Vertex.

13.2.2 Ethical Considerations

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

documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

13.2.3 Subject Information and Informed Consent

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

13.2.4 Investigator Compliance

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

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

13.2.5 Access to Records

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

13.2.6 Subject Privacy

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

For sites participating in the US, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated regulations, an executed HIPAA authorization will be obtained by the site from each subject (or the legal representative of the subject) before

research activities may begin. Each HIPAA authorization will comply with all HIPAA requirements including authorization allowing the site access to and use of the subject's personally identifiable health information, authorization for the site to disclose such information to Vertex, the FDA, and other parties requiring access under the protocol, and statements as to the purpose for which such information may be used and for how long.

13.2.7 Record Retention

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

13.2.8 Study Termination

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

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

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

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

13.2.9 End of Study

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

13.3 Data Quality Assurance

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

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each subject. Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure, validated, web-based electronic data capture (EDC) application. 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 or remote 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 or remote visits from a representative of Vertex or designee (study site monitor), who will review the CRFs/SAE Forms and source documents. The study site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

13.5 Electronic Data Capture

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

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

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

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

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

13.6 Confidentiality and Disclosure

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

The investigator understands that the information developed from this clinical study will be used by Vertex in connection with the development of the study drug and other drugs and diagnostics,

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

13.7 Publications and Clinical Study Report

13.7.2 Clinical Study Report

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

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX21-548-103	Version #: 3.0	Version Date: 17 February 2023
Study Title: A Phase 2, Randomized, Double-blind, Active-controlled, Dose-ranging, Parallel-design Study of the Efficacy and Safety of VX-548 in Subjects With Painful Diabetic Peripheral Neuropathy		

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

Printed Name	Title
Signature	Date

15.2 Investigator Signature Page

Protocol #: VX21-548-103	Version #: 3.0	Version Date: 17 February 2023
Study Title: A Phase 2, Randomized, Double-blind, Active-controlled, Dose-ranging, Parallel-design Study of the Efficacy and Safety of VX-548 in Subjects With Painful Diabetic Peripheral Neuropathy		

I have read Protocol VX21-548-103, Version 3.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-548 and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date