1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 2b/3, Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of VX-210 in Subjects With Acute Traumatic Cervical Spinal Cord Injury

Vertex Study Number: VX15-210-101

[redacted]

Date of Protocol: 14 April 2017 (Version 2.0)

Vertex Pharmaceuticals Incorporated
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2 PROTOCOL SYNOPSIS

Title

A Phase 2b/3, Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of VX-210 in Subjects With Acute Traumatic Cervical Spinal Cord Injury

Clinical Phase and Clinical Study Type

Phase 2b/3, efficacy and safety

Objectives

Primary Objectives:

Evaluation of the efficacy and safety of VX-210 treatment

Secondary Objectives:

- Neurological recovery: examination of the effects of VX-210 on the recovery of sensation and motor activity
- Daily function: analysis of the impact of VX-210 on activities of daily living and requirements for attendant care

Endpoints

Primary Endpoint:

Change from baseline in upper extremity motor score (UEMS) at 6 months after treatment

Secondary Endpoints:

- Spinal Cord Independence Measure (SCIM) III Self-Care subscore at 6 months after treatment
- Capabilities of Upper Extremity Test (CUE-T) score at 6 months after treatment
- Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) Quantitative Prehension score at 6 months after treatment
- American Spinal Injury Association Impairment Scale (AIS) grade conversion from baseline to 6 months after treatment
- Motor level change from baseline to 6 months after treatment
- Pharmacokinetic (PK) parameters of VX-210

[redacted]

Number of Subjects

Approximately 100 subjects: approximately 50 subjects per arm (9-mg VX-210 and placebo)

Study Population

- Male and female subjects 14 through 75 years of age with acute traumatic cervical spinal cord injury
- Motor level C4, C5, C6, or C7 (subset) on each side
- Scheduled and planned to undergo a spinal decompression/stabilization

surgery that commences within 72 hours after the initial injury
- AIS grade A or AIS grade B

Investigational Drug

Active substance: VX-210

Activity: inhibition of Rho GTPase

Strengths and route of administration:
- 9 mg and placebo
- One-time, direct, extradural administration on dura mater of the spinal cord during decompression/stabilization surgery

Study Duration

For an individual subject, the study will last approximately 12 months.

Study Design

In this multicenter, double-blind, placebo-controlled, Phase 2b/3 study, subjects will be randomized to receive a single 9-mg dose of VX-210 in fibrin sealant or a placebo (buffer solution) in fibrin sealant. The 1-time treatment (or placebo) will be administered by a surgeon directly to the dura mater of the spinal cord at the site of injury during decompression/stabilization surgery that commences within 72 hours after the initial injury. Follow-up assessments of recovery in VX-210-treated versus placebo-treated subjects will be conducted at 6 weeks, 3 months, 6 months, and 12 months after treatment.

Assessments

Safety:

Adverse events, vital signs, electrocardiograms, clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis), physical examinations, surgical site examinations, and immunogenicity measures

Efficacy:

International Standards for the Neurological Classification of Spinal Cord Injury examination, SCIM III, CUE-T, GRASSP Quantitative Prehension test, [redacted], hospitalizations, [redacted]

PK: Serum concentrations of VX-210

Statistical Analyses

Randomization: Subjects will be randomized to the 2 study arms at a 1:1 ratio.

Stratification: Subjects will be stratified by age (<30 versus ≥30 years of age) and AIS grade (A versus B with sacral pinprick preservation versus B without sacral pinprick preservation) when they are randomized to the 2 study arms.

Null Hypotheses: The mean change from baseline in UEMS at 6 months after treatment is the same for 9-mg dose of VX-210 and placebo.

Sample Size Considerations: If 9-mg dose group improves in UEMS by 4 points over placebo, a total of approximately 100 subjects (approximately 50/arm) will provide approximately 82.1% power to detect a statistically significant treatment effect for 9-mg dose group compared to placebo, considering the interim futility analysis.

Primary Analyses: The study will have an overall 2-sided type I error rate controlled at ≤0.05. The primary efficacy endpoint will be analyzed using a mixed-effects model for repeated measures. The model will include the change from baseline in UEMS as the dependent variable; treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect, with adjustment for age and AIS grade (A versus B with sacral pinprick preservation

versus B without sacral pinprick preservation) at baseline. The primary result obtained from the model will be the treatment effect at 6 months after treatment. Statistical significance for the primary efficacy endpoint will be tested between 9-mg dose group and the placebo group at significance level $\alpha = 0.05$.

Secondary Analyses: To control the type I error rate, a hierarchical testing procedure will be used for the important efficacy endpoints. At each step, the test for treatment effect will be considered statistically significant if the test meets the criteria for significance and all previous tests are also statistically significant. The first endpoint in the testing hierarchy will be the primary endpoint (change from baseline in UEMS at 6 months after treatment). The second endpoint in the testing hierarchy will be the SCIM III Self-Care subscore at 6 months after treatment.

IDMC Reviews Safety and tolerability data will be reviewed by an independent data monitoring committee to ensure the safety of the subjects in the study.

Results of an interim analysis for futility will be reviewed by the IDMC.

3 SCHEDULE OF ASSESSMENTS

The Schedule of Assessments is shown in Table 3-1.

Table 3-1 Study VX15-210-101 Schedule of Assessments

Event/Assessment	Screening[a]	Surgery[b]	Post-Surgery[c]	6-Week Follow-up (± 7 Days)[d]	3-Month Follow-up (± 7 Days)[d]	6-Month Follow-up (± 7 Days)[d]	12-Month Follow-up (± 7 Days)[d]	Early Termination[d]	Safety Follow-up 28 (± 3) Days After Treatment[d,e]
Informed consent	X								
Medical history	X								
Demographics	X								
Review of spine imaging	X								
Serum β-HCG (all female subjects)	X								
Serum FSH (postmenopausal female subjects <60 years only)	X[f]								
Height and weight	X								
Eligibility assessment	X								
Enrollment and randomization	X								

[a] Results of assessments performed as part of standard of care (with the exception of the ISNCSCI examination) within 72 hours after the initial injury and before signing of informed consent form may be carried forward as screening results.

[b] 'Surgery' in this table refers to the spinal decompression/stabilization surgery that commences within 72 hours after the initial injury during which the study drug (VX-210 or placebo) is administered in fibrin sealant.

[c] The Post-Surgery assessments will be performed within the time period following the completion of surgery and 7 days after surgery as specified in the footnotes for each individual assessment.

[d] Transportation to follow-up assessments will be available if required. Follow-up assessments of recovery will be conducted at 6 weeks, 3 months, 6 months, and 12 months after treatment.

[e] The Safety Follow-up Visit will be required in addition to the Early Termination Visit only for subjects who prematurely terminate from the study prior to Day 28 after treatment. Subjects who prematurely terminate from the study subsequent to Day 28 after treatment will only be required to complete the Early Termination Visit.

[f] Serum FSH assessment is only required when a waiver to contraception is sought. Only 1 serum FSH assessment is required, at Screening, Surgery, or Post-Surgery.

Table 3-1 Study VX15-210-101 Schedule of Assessments

Event/Assessment	Screening[a]	Surgery[b]	Post-Surgery[c]	6-Week Follow-up (± 7 Days)[d]	3-Month Follow-up (± 7 Days)[d]	6-Month Follow-up (± 7 Days)[d]	12-Month Follow-up (± 7 Days)[d]	Early Termination[d]	Safety Follow-up 28 (± 3) Days After Treatment[d,e]
Safety [redacted] Assessments									
Physical examination[g]	X							X	X
Examination of surgical site			X[h]	X	X	X		X	X
Vital signs[g]	X							X	X
Standard 12-lead ECG[i]	X		X[j]						
Serum chemistry and hematology	X		X[k]	X	X			X	X
Coagulation studies	X		X[k]						
Urinalysis	X		X[k]						
[redacted]									
Serum samples for immunogenicity tests[m]	X		X[n]	X	X	X			

[g] Vital signs and full physical examinations will be performed at Screening, Early Termination, and Safety Follow-up Visits as applicable; symptom-directed vital signs and symptom-directed physical examinations will be performed at other study visits. Vital signs will be assessed following a 5-minute rest in the supine position.

[h] The Post-Surgery examination of surgical site will be performed within the time period following the completion of surgery and 7 days after surgery.

[i] The subject will be instructed to rest in the supine position for at least 5 minutes before having an ECG performed. The ECG will be performed before any other procedures that may affect heart rate, such as blood draws. Additional ECGs are to be performed as appropriate (see Section 11.6.4).

[j] The Post-Surgery ECGs will be obtained between 4 and 6 hours and between 12 and 14 hours after treatment.

[k] The Post-Surgery clinical laboratory tests will be collected between 24 and 48 hours after treatment.

[redacted]

[m] Serum samples for immunogenicity tests will also be collected at the time of any SAE occurring within 3 days after treatment.

[n] The Post-Surgery serum sample for immunogenicity tests will be collected 7 days after treatment or upon hospital discharge if discharge occurs earlier than 7 days after treatment.

Table 3-1 Study VX15-210-101 Schedule of Assessments

Event/Assessment	Screening[a]	Surgery[b]	Post-Surgery[c]	6-Week Follow-up (± 7 Days)[d]	3-Month Follow-up (± 7 Days)[d]	6-Month Follow-up (± 7 Days)[d]	12-Month Follow-up (± 7 Days)[d]	Early Termination[d]	Safety Follow-up 28 (± 3) Days After Treatment[d,e]
Adverse events and prior and concomitant medications and procedures	Continuous from signing of ICF through the last study visit								
Efficacy Assessments									
ISNCSCI examination°	X			X	X	X	X	X	X
SCIM III°				X	X	X	X	X	X
GRASSP Quantitative Prehension°						X		X	X
CUE-T°						X		X	X
[redacted]									
Hospitalizations	Continuous from signing of ICF through the last study visit								
Study Drug Administration									
VX-210 or placebo		X							
Pharmacokinetic Assessments									
Serum samples for PK	X[q]	X[q]	X[q]						

° Conducted by an independent, trained assessor (e.g., physiatrist/occupational therapist/physical therapist).

[redacted]

Serum samples for PK analyses will be collected at ≤72 hours (before surgery) and at 3, 6, 12, 24, and 48 hours after treatment and at the time of any SAE occurring within 3 days after treatment. The acceptable window for the post-treatment PK sampling time points is ± 30 minutes.

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5 INTRODUCTION

5.1 Introduction

5.1.1 Overview of SCI

A traumatic lesion to the spinal cord results in paralysis below the level of the injury. More than 17,000 individuals in the US per year suffer spinal cord injuries (SCIs) from motor vehicle accidents (38%), falls (30.5%), violence (13.5%), sports (9%), medical or surgical accidents (5%), or other causes (4%).[1] Approximately half of SCIs in the US are cervical[1,2], and complete cervical SCI leads to lifelong quadriplegia. Individuals with complete cervical SCI are therefore often unable to independently conduct activities of daily living (ADLs), and may require up to 24-hour attendant care.[3,4] Individuals with SCI also face serious comorbidities, including autonomic dysreflexia[5], bladder dysfunction[6], osteoporosis[7], pressure sores[8], reduced immune function[9], chronic lifelong pain[10], and cardiovascular complications.[11] Based on these comorbidities and post-SCI paralysis, the lifespan of individuals with cervical SCI is substantially shorter than the lifespan for those without SCI.[1]

5.1.2 Lack of Available Treatments for SCI

There are no approved treatments to restore motor function after SCI. Currently, decompression/stabilization surgery is widely recognized as standard of care in the management of acute traumatic SCI to alleviate pressure within the spinal cord and prevent further lesion-induced nervous tissue damage.[12] Individuals with SCI are also commonly given methylprednisolone, although the impact of this drug on recovery from paralysis is controversial.[13] Spinal cord injuries, therefore, represent a high unmet medical need where small improvements in function can have a large impact on well-being.

5.1.3 Scientific Rationale for VX-210 Development

The inability of patients to recover motor function after SCI stems, in part, from the failure of neurons in the central nervous system (CNS) to regrow their axons after injury. Axon regeneration is impeded by a number of growth-inhibiting factors.[14,15] These factors stimulate an intracellular master enzyme, Rho[16,17], which leads to a cascade of events culminating in collapse of the neuronal growth cone[18] and a failure of injured axons to regenerate.[14,15] Inhibition of Rho activity represents a potential treatment for CNS injuries such as SCI.

VX-210 is a protein derivative of C3 transferase that inhibits Rho [redacted] In rodent models of SCI, this stimulates axon regeneration and plasticity,[20,21] and decreases secondary tissue damage and glial scarring at the injury site.[20,22,23,24] These neuroregenerative and neuroprotective effects combine to promote functional recovery after SCI in rodents.[20,22,25] Therefore, in humans with acute SCI, the expected effect of VX-210 is the recovery of motor function.

6 STUDY OBJECTIVES

6.1 Primary Objectives

The evaluations of the efficacy and safety of VX-210 treatment are the primary objectives of the study.

6.2 Secondary Objectives

- Neurological recovery: examination of the effects of VX-210 on the recovery of sensation and motor activity
- Daily function: analysis of the impact of VX-210 on ADLs and requirements for attendant care

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Change from baseline in upper extremity motor score (UEMS) at 6 months after treatment is the primary endpoint of the study.

7.2 Secondary Endpoints

7.2.1 Secondary Endpoints

- Spinal Cord Independence Measure (SCIM) III Self-Care subscore at 6 months after treatment
- Capabilities of Upper Extremity Test (CUE-T) score at 6 months after treatment
- Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) Quantitative Prehension score at 6 months after treatment
- American Spinal Injury Association Impairment Scale (AIS) grade conversion from baseline to 6 months after treatment
- Motor level change from baseline to 6 months after treatment
- Pharmacokinetic (PK) parameters of VX-210

[redacted]

8 STUDY DESIGN

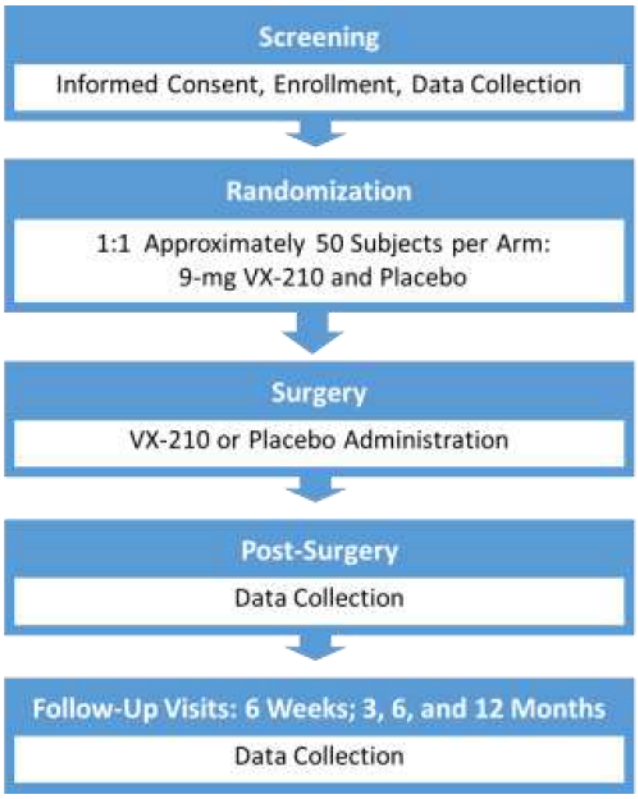
8.1 Overview of Study Design

This is a multicenter, randomized, double-blind, placebo-controlled study to examine the efficacy and safety of VX-210 treatment. The study will be conducted at approximately 45 sites in the United States and Canada and will enroll approximately 100 male or female subjects 14 to 75 years of age (inclusive) with acute traumatic SCI, C4 to C7 (motor level) on each side, and AIS grade A or AIS grade B. Subjects will be randomized to receive a single 9-mg dose of VX-210 in fibrin sealant or a placebo (buffer solution) in fibrin sealant at a 1:1 ratio until approximately 100 subjects are enrolled (approximately 50 subjects in each treatment arm: 9-mg VX-210 and placebo). Subjects will be stratified by age (<30 versus ≥30 years of age) and AIS grade (A versus B with sacral pinprick preservation versus B without sacral pinprick preservation) when they are randomized to the 2 study arms. The 1-time dose of VX-210 or placebo will be administered by a surgeon directly to the dura mater of the spinal cord at the site of injury during decompression/stabilization surgery that commences within 72 hours after the initial injury.

For an individual subject, the study will last approximately 12 months. Follow-up appointments after the initial hospital stay will be at 6 weeks, 3 months, 6 months, and 12 months after treatment. At specified time points during the study, subjects will be evaluated for medical, neurological, and functional changes, and serum will be collected for PK and immunological analyses (Table 3-1).

A schematic of the study design is provided in Figure 8-1.

Figure 8-1 Schematic of Study Design



8.1.1 Screening Assessments

Screening assessments are listed in Table 3-1.

The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from each subject or legally authorized representative.

Results of assessments performed as part of standard of care (with the exception of the ISNCSCI examination) within 72 hours after the initial injury and before signing of informed consent form may be carried forward as screening.

8.1.2 Surgery and Post-Surgery

Surgery and post-surgery assessments are listed in Table 3-1.

VX-210 or placebo will be administered by a surgeon as a 1-time, topical dose to the dura mater of the spinal cord at the site of injury during the subject's decompression/stabilization surgery. A fibrin sealant vehicle will be used for delivery. For details on administration see Section 10.2.

8.1.3 Follow-up

Follow-up assessments and timepoints are listed in Table 3-1. Transportation for subjects to the site for follow-up assessments will be available if required.

8.1.4 Early Discontinuation

Early Termination Visit will be conducted when a subject withdraws or is withdrawn from the study (Section 9.4), or 1 or multiple study sites are closed (Section 13.2.7). Assessments at the Early Termination Visit are listed in Table 3-1. The Safety Follow-up Visit will be required in addition to the Early Termination Visit only for subjects who prematurely terminate from the study prior to Day 28 after treatment. Subjects who prematurely terminate from the study subsequent to Day 28 after treatment will only be required to complete the Early Termination Visit.

8.1.5 Independent Data Monitoring Committee

Safety and tolerability data will be reviewed by an independent data monitoring committee (IDMC) to ensure the safety of the subjects in the study (Section 12.3.5.2). Results of an interim analysis for futility (Section 12.3.5.1) will be reviewed by the IDMC. Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be included in the IDMC charter. The IDMC charter will be finalized before the first subject is screened in the study.

8.2 Rationale for Study Design and Study Drug Regimens

8.2.1 Rationale for Study Design

The design for this study was developed using guidelines from the International Campaign for Cures of Spinal Cord Injury Paralysis[3,26,27,28], as well as more recent examinations of functionally meaningful efficacy endpoints for SCI clinical studies.[4,29,30]

The rationale for study drug dose and duration are described in Section 8.2.2.

The primary and secondary endpoints will provide evidence of whether VX-210 offers a meaningful benefit compared to placebo. The rationale and background for the primary and secondary efficacy assessments are provided in Section 8.2.3.

8.2.2 Rationale for Study Drug Dose and Duration

VX-210 is administered as a 1-time, topical dose to the dura mater of the spinal cord, as an adjunct to decompression/stabilization surgery.[31] For delivery, VX-210 is reconstituted in a fibrin sealant [redacted]. After administration, the VX-210 sealant solution polymerizes into a fibrin gel, from which VX-210 is expected to be released into the surrounding tissues over the next several hours. This non-invasive, 1-time administration requires no additional surgery or hospitalization and eliminates the risk of further spinal cord damage from needle insertion.

An open-label, dose-escalation Phase 1/2a study (Protocol Number: BA-210-101) to evaluate the safety and tolerability of VX-210 as a treatment for SCI was conducted at 9 sites in the United States and Canada.[7,31] The study enrolled 48 men and women, ages 16 to 70 years inclusive, with acute AIS A cervical SCIs (n = 16) or acute AIS A thoracic SCIs (n = 32). Five doses of VX-210 were tested (0.3, 1, 3, 6, and 9 mg). VX-210 doses were reconstituted in a fibrin sealant and administered to the dura mater of the spinal cord in a single, extradural dose, as an adjunct to decompression/stabilization surgery. No study serious adverse events (SAEs) were assessed as related to VX-210, and preliminary efficacy analyses showed a

trend toward a reduction in paralysis in cervical subjects in comparison with historical controls.[7,31]

The 9-mg dose was selected to maximize target engagement. Details of relevant clinical and nonclinical studies are provided in the Investigator's Brochure.

8.2.3 Rationale for Study Assessments

The safety and PK assessments are standard parameters for clinical studies in drug development. The scope of the assessments is considered appropriate for safety monitoring in the context of this study. Immunogenicity testing will enable evaluation of the immune response to VX-210.

Vertex has carefully selected the following efficacy assessments based on guidance from international panels [4,27], input from key opinion leaders, and the recent review of SCI Common Data Elements by the National Institute of Neurological Disorders and Stroke.

The efficacy endpoints and associated assessments are summarized in Table 8-1.

8.2.3.1 Primary Endpoint

Upper Extremity Motor Score

UEMS is a subset of the ISNCSCI examination, an assessment developed by the American Spinal Injury Association (ASIA) that is widely used for evaluating efficacy in SCI clinical trials.[27]

The upper extremity motor score focuses selectively on the hand and arm control most relevant to individuals with a cervical spinal cord injury.[32] Muscle contraction strength is graded in 5 key arm and hand muscle groups on each side of the body from 0 (total paralysis) to 5 ([normal] active movement), for a total possible UEMS score of 50. Importantly, UEMS has been shown to measure neurological recovery in a manner that correlates with improvement on functional tests.[30,33,34,35,36] As each of the muscles measured in the UEMS assessment is critical for daily function, small increases in UEMS can correspond to a significant improvement in functional recovery.[30,37] The ISNCSCI scoresheet is provided in Section 15.1.

8.2.3.2 Secondary [redacted]

The Spinal Cord Independence Measure III

The SCIM III[38,39,40] is an SCI-specific disability scale viewed as the most sensitive, reliable, and relevant test for assessing function after SCI.[12,41] The Self-Care section of the SCIM III is a 20-point subscale that specifically examines a subject's ability to feed, dress, groom, and bathe themselves on a daily basis. This subscale is often evaluated as a measure of the ability to perform ADLs dependent on the changes in hand and arm control most relevant to the cervical SCI population. The SCIM III Self-Care subscore will be a secondary endpoint.

[redacted]

Capabilities of Upper Extremity Test

The CUE-T[42] is a functional test [35,42] that measures a subject's ability to perform specific functional movements/tasks with the arms and hands (e.g., grasping a pencil, pushing or lifting a weight). The total possible score is 128 (after proper score conversion of all 32 items to a 0 to 4 scale). The CUE-T scoresheet is provided in the study reference manual.

GRASSP Quantitative Prehension Test

GRASSP Quantitative Prehension Test [43] is a functional test [34,43,44,45,46] that ranks a subject's ability to perform specific functional tasks with the arms, hands, and fingers (e.g., turning a key in a lock, pouring water in a cup). The total possible score is 60. The GRASSP Prehension scoresheet is provided in Section 15.3.

Other Common Derivatives of the ISNCSCI Assessment

The ASIA Impairment Scale (AIS) ranks impairment according to body-wide motor/sensory results (see ISNCSCI Scoresheet in Section 15.1 for additional details):

- **AIS A**; **Complete:** No sensory or motor function is preserved in the sacral segments S4 to 5.
- **AIS B**; **Sensory Incomplete:** Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4 to 5 (light touch or pin prick at S4 to 5 or deep anal pressure) AND no motor function is preserved more than 3 levels below the motor level on either side of the body.
- **AIS C**; **Motor Incomplete:** Motor function is preserved at the most caudal sacral segments for voluntary anal contraction OR the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments (S4 to S5) by light touch, pin prick, or deep anal pressure) and has some sparing of motor function more than 3 levels below the ipsilateral motor level on either side of the body (This includes key or non-key muscle functions to determine motor incomplete status). For AIS C – less than half of key muscle functions below the single neurological level of injury have a muscle grade ≥3.
- **AIS D; Motor Incomplete:** Motor incomplete status as defined above, with at least half (half or more) of key muscle functions below the single neurological level of injury having a muscle grade ≥3.
- **AIS E; Normal:** If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient has prior deficits, then the AIS grade is E. Someone without an SCI does not receive an AIS grade.

  Using "Not Determined" (ND): To document the ASIA Impairment Scale grade when it is unable to be determined based on the examination results.

Conversion of 2 or more AIS grades has been used previously as a clinical assessment of significant neurologic recovery.[47,48]

The motor level for the right or left side is defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), provided the key muscle functions represented by

segments above that level are judged to be intact (graded as a 5). Note: In regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal. The motor level is determined for both the right and left sides of the body; the right and left motor level may be different. For additional details, please see the ISNCSCI Scoresheet in Section 15.1. An improvement of 2 or more motor levels on either side has been shown to correlate with functional improvements.[4,30]

[redacted]

Table 8-1 Summary of Efficacy Endpoints and Assessments

Efficacy Endpoint	Efficacy Assessment
Primary Endpoint	
Change from baseline in upper extremity motor score (UEMS) at 6 months after treatment	ISNCSCI examination
Secondary Endpoints	
Spinal Cord Independence Measure (SCIM) III Self-Care subscore at 6 months after treatment	SCIM III
Capabilities of Upper Extremity Test (CUE-T) score at 6 months after treatment	CUE-T
Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) Quantitative Prehension score at 6 months after treatment	GRASSP Quantitative Prehension Test
American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade conversion from baseline to 6 months after treatment	ISNCSCI examination
Motor level change from baseline to 6 months after treatment	ISNCSCI examination

[redacted]

[redacted]

9 STUDY POPULATION

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

9.1 Inclusion Criteria

Subjects who meet all of the following inclusion criteria will be eligible.

1. Subject (or a witness, or his or her legally appointed and authorized representative) will sign and date an informed consent form (ICF).
2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, contraceptive guidelines, and other study procedures.
3. Subjects are male or female between 14 and 75 years of age, inclusive.
4. Acute traumatic cervical SCI, motor level of C4, C5, C6, or C7 on each side:
   - Screening UEMS score must be ≤16 points on each side.
   - AIS A subjects with a C4 motor level on both sides must have at least 1 point of motor activity between C5 and T1 on at least 1 side.
   - AIS B subjects with a C4 motor level on both sides must have at least 1 point of motor activity between C5 and C7 on at least 1 side.
5. AIS grade A or AIS grade B.
6. Scheduled and planned to undergo a spinal decompression/stabilization surgery that commences within 72 hours after the initial injury.
7. Computed tomography (CT) scan or magnetic resonance imaging (MRI) is consistent with the subject's neurological deficit.

9.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be eligible.

1. Participation in any other clinical study for acute SCI without approval by the sponsor (Vertex).
2. Inability to undergo decompression/stabilization surgery that commences within 72 hours after injury.

3. One or more upper extremity muscle groups untestable during screening ISNCSCI examination.
4. Acute SCI from gunshot or penetrating/stab wound; non-traumatic SCI (e.g., transverse myelitis, acute disc herniation); brachial plexus injury; complete spinal cord transection; or multifocal SCI.
5. Females who are breastfeeding or have a positive serum pregnancy test.
6. Body mass index (BMI) of $\geq$40 kg/m^2 at screening.
7. History of an adverse reaction to a fibrin sealant or its human or bovine components.
8. Unconsciousness or other mental impairment that precludes reliable ISNCSCI examination.
9. Known immunodeficiency, including human immunodeficiency virus, or use of immunosuppressive or cancer chemotherapeutic drugs.
10. Any significant medical or psychiatric comorbidities (e.g., neurologic, cardiac, respiratory, hepatic, bleeding/coagulation disorder, renal, active malignancy) that would significantly increase the risk of study enrollment and/or significantly interfere with study outcomes or assessments, in the judgment of the investigator. (Note: Subjects with chronic medical conditions that are well controlled are eligible for the study: e.g., a subject with mild and well-controlled asthma or diabetes would be eligible, whereas a subject with severe congestive heart failure limiting activity or severe cardiopulmonary disorder limiting exercise would not be eligible.)
11. 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.

9.3 Prior and Concomitant Medications

Intravenous steroid medications (e.g., methylprednisolone) for the treatment of SCI are permitted. At screening, all medications received in the past 30 days will be collected. Information regarding all concomitant medications administered from screening through the end of study participation will be collected.

9.4 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from the study at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. If a subject has been withdrawn from the study, the subject should continue to be followed, provided the subject has not withdrawn consent.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return for an Early Termination Visit and/or Safety Follow-up Visit, as applicable (see Section 8.1.4), and follow up with the subject regarding any unresolved AEs.

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

9.5 Replacement of Subjects

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

10 STUDY DRUG ADMINISTRATION AND MANAGEMENT

10.1 Preparation and Dispensing

VX-210 or placebo will be provided to study sites in a blinded fashion. Each individual 2 mL glass vial will contain 0.5 mL of blinded clinical study material.

The fibrin sealant delivery vehicle [redacted] will be provided as a single-use kit, consisting of 4 components packed in separate vials.

Additional details regarding packaging, labeling, and dispensing for VX-210 will be included in the Pharmacy Manual.

Additional details regarding preparation of VX-210/placebo [redacted] are provided in the Formulation Preparation Instructions.

10.2 Administration

Each subject will receive 1 single dose of VX-210 or placebo in fibrin sealant. The single dose of VX-210 or placebo in fibrin sealant will be administered during decompression/stabilization surgery that commences within 72 hours after the initial injury.

VX-210 or placebo in fibrin sealant will be delivered topically to the dural surface of the spinal cord at the site of injury (local, extradural administration). The start time of application of clinical study material must be collected. Presence of dural tears will be collected.

Administration details will be provided in the Surgical Guidelines.

10.3 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized to receive a single 9-mg dose of VX-210 in fibrin sealant, or a placebo (buffer solution) in fibrin sealant at a 1:1 ratio. Subjects will be stratified by age (<30 versus ≥30 years of age) and AIS grade (A versus B with sacral pinprick preservation versus B without sacral pinprick preservation) when they are randomized to the 2 study arms.

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 dummy randomization list. The final randomization list will be generated and approved by an unblinded biostatistician or designee who is not a member of the study execution team.

10.4 Dose Modification for Toxicity

This is a single-dose study. No dose modifications for toxicity are allowed or required.

10.5 Packaging and Labeling

Vertex will supply VX-210 or placebo in 2.0 mL glass vials (Table 10-1). Blinded study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for VX-210 will be included in the Pharmacy Manual.

[redacted]

10.6 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 drug accountability forms as instructed by Vertex.

Table 10-1 Study Drug

Drug Name	Formulation/ Route	Dosage	Packaging	Storage Condition
VX-210	VX-210 drug product in 5 mM sodium citrate buffer to be reconstituted in fibrin sealant [redacted] before 1-time extradural administration	9-mg	2.0 mL glass vials containing 0.5 mL of frozen VX-210 at 30 mg/mL (15 mg VX-210/vial)	According to the container label
Placebo	Sodium citrate buffer to be reconstituted in fibrin sealant [redacted] before 1-time extradural administration	--	2.0 mL glass vials containing 0.5 mL of frozen sodium citrate buffer	According to the container label

10.7 Drug Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of study drug administered. Study drug will be retained at the site according to instructions provided by Vertex or its designee until inventoried by the study monitor. The study monitor will review study drug records and inventory throughout the study.

10.8 Disposal, Return, or Retention of Unused Drug

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

10.9 Compliance

The single study drug dose is administered during the inpatient period of the study by the investigator or designee. Guidance on investigator compliance can be found in Section 13.2.3.

10.10 Blinding and Unblinding

This will be a randomized, double-blind study.

10.10.1 Blinding

All Vertex study personnel will be blinded to subject treatment assignments, except for the following individuals: an external vendor biostatistician preparing the final (production) randomization list who is not part of the SET; Bioanalytical CRO analyzing PK samples and the Vertex Bioanalytical staff who needs to review the raw data from Bioanalytical CRO (excluding Bioanalytical SET member who will continue to be blinded); and Vertex Global Patient Safety (GPS) and Regulatory Affairs representatives when required to satisfy regulatory reporting requirements.

10.10.2 Unblinding

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

Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators will use their best judgment as to whether to unblind without first attempting to contact the medical monitor to discuss and agree to the need for unblinding. If investigators deem it not necessary to unblind immediately, they will first attempt to contact the medical monitor to discuss and agree to the need for unblinding. If investigators have tried, but are unable to reach the medical monitor, they will use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the medical monitor.

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

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

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

definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS or designee, per Section 13.1.2.

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

11 ASSESSMENTS

11.1 Timing of Assessments

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

11.2 Subject and Disease Characteristics

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

11.3 Pharmacokinetics

11.3.1 Serum Sampling

Serum samples for the determination of the concentrations of VX-210 will be collected at visits indicated in Table 3-1 and at the time of any SAE occurring within 3 days after treatment.

The acceptable window for the post-treatment PK sampling time points is ± 30 minutes. Samples collected outside this window will be considered a protocol deviation. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing.

The following will be recorded accurately in the source document: date and time of administration of the dose; date and time of each of the PK serum samples.

11.3.2 Processing and Handling of Pharmacokinetic Samples

Detailed procedures for the collection of serum samples and further procedures for processing and handling of samples for PK analysis will be provided in the Laboratory Manual and/or Sample Handling Guidelines. The shipment address and assay laboratory contact information will be provided to the investigational site before initiation of the study.

11.3.3 Bioanalysis

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

[redacted]

11.5 Efficacy

For all assessments, all efforts will be made to use the same assessor for a given examination for a given subject.

11.5.1 ISNCSCI Examination

The ISNCSCI examination will be conducted at time points indicated in Table 3-1 and will be conducted by an independent, trained assessor. All efforts will be made to use the same assessor for all ISNCSCI examinations for a given subject. All trained assessors must meet Vertex requirements provided in the Assessment Handbook and must complete required training.

In addition to providing detailed motor and sensory scores, this assessment will determine the right and left motor levels, AIS Grade, neurological level, and complete/incomplete status.

Specifics on proper ISNCSCI administration will be provided in the Assessment Handbook.

11.5.2 The Spinal Cord Independence Measure III

The SCIM III survey will be administered at the time points indicated in Table 3-1 by an independent, trained assessor. All efforts will be made to use the same assessor for all SCIM III examinations for a given subject. All trained assessors must meet Vertex requirements provided in the Assessment Handbook and must complete required training.

This functional assessment measures (1) self-care abilities (feeding, dressing, grooming, bathing); (2) respiration and sphincter management; and (3) mobility.

Specifics on proper SCIM III administration will be provided in the Assessment Handbook.

11.5.3 Capabilities of Upper Extremity Test

The CUE-T assessment will be conducted at the time points indicated in Table 3-1 and will be conducted by an independent, trained assessor. All trained assessors must meet Vertex requirements provided in the Assessment Handbook and must complete required training.

This test measures reaching capabilities and the ability to perform specific functional tasks with the hands and arms (e.g., grasping a pencil, pushing/lifting a weight).

Specifics on proper CUE-T administration will be provided in the Assessment Handbook.

11.5.4 GRASSP Quantitative Prehension Test

The GRASSP Quantitative Prehension test will be conducted at the time points indicated in Table 3-1 and will be conducted by an independent, trained assessor. All trained assessors must meet Vertex requirements provided in the Assessment Handbook and must complete required training.

This test measures a subject's ability to perform specific functional tasks with the hands/arms (e.g., pouring water from bottle, screwing nuts on bolts).

Specifics on proper GRASSP Quantitative Prehension Test administration will be provided in the Assessment Handbook.

11.5.7 Hospitalizations

At visits indicated in Table 3-1, subjects will be queried about hospitalizations. The dates for hospitalizations (i.e., dates of admission and discharge) and the reasons will be collected.

[redacted]

11.6 Safety

Safety evaluations will include AEs, vital signs, electrocardiograms (ECGs), clinical laboratory assessments, physical examinations, surgical site examinations, and immunogenicity measures.

11.6.1 Adverse Events

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

11.6.2 Clinical Laboratory Assessments

Blood and urine samples for safety assessment will be analyzed at each site's local laboratory. See the following sections for details regarding collection of blood samples for immunogenicity (Section 11.6.6), PK (Section 11.3), [redacted]

Blood samples for clinical laboratory assessments will be collected at time points indicated in Table 3-1. After screening, laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

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

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen	Erythrocytes	Nitrite
Creatinine	Mean corpuscular hemoglobin	Urobilinogen
Sodium	Mean corpuscular hemoglobin concentration	Urine protein
Potassium	Mean corpuscular volume	pH
Calcium	Platelets	Urine blood
Chloride	Leukocytes	Specific gravity
Magnesium	Differential (absolute and percent):	Urine ketones
Bicarbonate	Eosinophils	Urine bilirubin
Inorganic phosphate	Basophils	Urine glucose
Total bilirubin, direct bilirubin	Neutrophils	
Alkaline phosphatase	Lymphocytes	
Aspartate aminotransferase (= SGOT)	Monocytes	
Alanine aminotransferase (= SGPT)	**Coagulation Studies**	
Amylase	Activated partial thromboplastin time	
Lipase	Prothrombin time	
Gamma glutamyl transferase	Prothrombin time International Normalized Ratio	
Total protein		
Albumin		
Creatine kinase .		
Uric acid		
Cholesterol		

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis
Triglycerides Low-density lipoprotein High-density lipoprotein		

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

- Serum beta-human chorionic gonadotropin (ßHCG) for all female subjects
- Serum follicle-stimulating hormone (FSH) for suspected postmenopausal female subjects <60 years of age when a waiver to contraception is sought. Levels will be within the laboratory's range for postmenopausal for subjects to be considered of non-childbearing potential.

Clinical laboratory assessments from screening will have no clinically significant findings that preclude participation in the study, as judged by the investigator, for a subject to receive study drug.

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

11.6.3 Vital Signs and Surgical Site and Physical Examinations

The surgical site will be examined for proper wound healing and lack of infection at time points indicated in Table 3-1.

A physical examination of all body systems and vital signs assessments will be performed at the Screening, Early Termination, and Safety Follow-up Visits (see Table 3-1). At other visits, symptom-directed physical examinations and symptom-directed vital sign assessments can be performed at the discretion of the investigator or healthcare provider.

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

Vital signs include blood pressure (systolic and diastolic), temperature, pulse rate, and respiration rate. These will be assessed following a 5-minute rest in the supine position. After screening, any clinically significant findings in vital signs will be reported as AEs.

11.6.4 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout according to the Schedule of Assessments (Table 3-1). Additional standard 12-lead ECGs will be performed at any other time if clinically indicated. The performance of all ECGs will adhere to the following guidelines:

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

The ECG traces will be manually read at the study site by the PI or designee (e.g., qualified cardiologist). 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 will be recorded as AEs.

To ensure safety of the subjects, a qualified individual at the study site will make comparisons to baseline measurements. If the QTcF is increased by >45 msec from the baseline or an absolute QTcF value is ≥500 msec for any scheduled ECG, 2 additional ECGs will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>45 msec from baseline or ≥500 msec), continuous 3- or 5-lead ECG monitoring should be performed until QTcF values fall below the threshold value that triggered the repeat measurement, followed by a single ECG to confirm. If the subject is no longer on continuous monitoring, a single 12-lead ECG will be performed at least every 8 to 12 hours until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. If QTcF values do not return to baseline within 72 hours after administration of study drug, further monitoring will be done as clinically indicated.

11.6.5 Contraception and Pregnancy

11.6.5.1 Contraception

At this stage in the development of VX-210, study participation requires a commitment from the subject and his/her partner to use 2 methods of birth control. Acceptable methods of contraception for subjects and their partners are listed below.

Contraception for the couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- The male subject is infertile (e.g., bilateral vasectomy, as described in "acceptable contraceptive methods" below).
- The female subject 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 months and have a serum FSH level within the laboratory's reference range for postmenopausal females; the FSH requirement is waived for female subjects ≥60 years of age.
    - Documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy

    All other female subjects (including subjects with bilateral tubal ligations <6 months before administration of study drug and subjects who do not have a documented

hysterectomy or bilateral oophorectomy/salpingo-oophorectomy) will be considered to be of childbearing potential.

Acceptable Contraceptive Methods:

Acceptable contraceptive methods for **male subjects** or **male partners** of female subjects include the following:

- Documented bilateral vasectomy at least 6 months before administration of study drug, with a negative post-vasectomy semen analysis for sperm
- Barrier contraception (such as diaphragm, cervical cap, or female condom) with spermicide (if available). If spermicide is not available then 2 methods of contraception, one of which includes a condom, must be used (e.g., condom plus diaphragm, condom plus cervical cap). Local regulations may require use of an additional acceptable method of contraception.

Acceptable contraceptive methods for **female subjects** and **female partners** of male subjects include the following:

- Documented bilateral tubal ligation performed 6 months or more before administration of study drug.
- Oral, transdermal, injectable, or implantable hormonal birth control method successfully used for at least 60 days before administration of study drug.
- An intrauterine device (nonhormone-releasing) in place for at least 90 days before administration of study drug.
- Barrier contraception (such as diaphragm, cervical cap, or female condom) with spermicide (if available). If spermicide is not available then 2 methods of contraception, one of which includes a condom, must be used (e.g., condom plus diaphragm, condom plus cervical cap.) Local regulations may require use of an additional acceptable method of contraception.

Additional notes:

- Female condom cannot be used with male condom (as a double method of contraception) due to risk of tearing.
- All contraceptive methods will be used throughout the study.
- Male subjects will not donate sperm for 90 days after administration of study drug.

11.6.5.2 Pregnancy

Subjects will be counseled to inform the investigator of any pregnancy that occurs during the study.

If a subject or the female partner of a male subject becomes pregnant during the study, the investigator will notify the medical monitor and Vertex GPS within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form.

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

11.6.6 Immunogenicity Measures

11.6.6.1 Serum Sampling

Serum samples will be collected at visits indicated in Table 3-1 and will also be collected at the time of any SAE occurring within 3 days after treatment.

The following will be recorded accurately in the source document: date and time of administration of the dose; date and time of each of the immunogenicity serum samples.

11.6.6.2 Processing and Handling of Immunogenicity Samples

Detailed procedures for the collection of serum samples and further procedures for processing and handling of samples for immunogenicity analysis will be provided in the Laboratory Manual and Sample Handling Guidelines. The shipment address and assay laboratory contact information will be provided to the investigational site before initiation of the study.

11.6.6.3 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.

12 STATISTICAL AND ANALYTICAL PLANS

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

12.1 Sample Size and Power

The primary efficacy endpoint is the change from baseline in UEMS at 6 months after treatment.

The null hypothesis to be tested is that the mean change from baseline in UEMS at 6 months after treatment is the same for 9-mg dose of VX-210 and placebo. This null hypothesis will be tested at 2-sided significance level $\alpha = 0.05$.

The sample size was calculated using a projected standard deviation (SD) of 6.0, based on the variability of improvement in UEMS scores of cervical subjects in the historical Sygen database. Anticipated withdrawal of 10% of subjects before the first follow-up assessment was also included in the sample size calculation.

If 9-mg dose group improves in UEMS by 4 points over placebo (a clinically meaningful increase), a total of approximately 100 subjects (approximately 50 per arm) will have

approximately 82.1% power to detect a statistically significant treatment effect for 9-mg dose group compared to placebo, considering the interim futility analysis.

Based on the review of data from Anderson et al.,[38] the SD was projected to be 3.8 for SCIM III Self-Care subscore. Table 12-1 presents the estimated power for detecting different treatment differences between an active treatment group and the placebo group in SCIM III Self-Care subscore, assuming 45 randomized subjects with follow-up assessment in each treatment group without considering the possible power loss from the interim futility analysis.

Table 12-1 Power Estimates Under a Variety of Treatment Differences, Given 45 Randomized Subjects With Follow-up Assessments in Each Treatment Group

Mean Difference in SCIM III Self-Care Subscore	Power (%)
1	23
2	69
3	95

Power estimates are based on 2-sided t-test with $\alpha = 0.05$.

12.2 Analysis Sets

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

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

The Full Analysis Set (FAS) is defined as all randomized subjects who have received study drug. The FAS is to be used in efficacy analyses in which subjects will be analyzed according to their randomized treatment group and not to the treatment they actually received.

The Safety Set is defined as all subjects who have received study drug. The Safety Set is to be used for all safety analyses in which subjects will be analyzed according to the treatment they received and not according to their randomized treatment group.

12.3 Statistical Analysis

The primary objectives of this study are to evaluate the efficacy and safety of VX-210 treatment in subjects with acute traumatic cervical SCI. The primary analyses will be based on the 6 month data. [redacted]

This section presents a summary of the planned statistical analyses of efficacy and safety for this study. The Vertex Biometrics department or a designated CRO will analyze the data derived from this study. Statistical Analysis System Version 9.2 or higher will be used to generate all statistical outputs (tables, figures, listings, and data sets).

Statistical analysis and presentation details will be provided in the SAP for the study.

12.3.1 General Considerations

All individual subject data for all individual subjects randomized or received study drug will be presented in data listings.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, standard error (SE), median, minimum value (min), and maximum value (max). The precision of the measurement for each continuous variable will be used to determine the number of decimal places to present in tables, figures, and derived listings. Unless otherwise specified, min and max values will be reported with the same precision as the units of measure; the mean, median, SD, and SE will be reported to 1 greater decimal place. Any values that require transformation to standard units (metric or International System [SI]) will be converted with the appropriate corresponding precision. Details will be provided in the SAP.

Categorical variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place.

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

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

The treatment-emergent (TE) period will include the time from dosing with study drug to the Safety Follow-up Visit or 28 days after treatment for subjects who do not have a Safety Follow-up Visit.

12.3.2 Background Characteristics

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, and other background characteristics will be summarized. Additionally, all subject data will be presented in subject data listings. All summaries will be based on the FAS, unless otherwise specified in the SAP for the study. No statistical hypothesis testing will be performed on background characteristics.

12.3.2.1 Subject Disposition

Number and percentage of subjects in the following categories will be summarized as appropriate:

- Randomized or dosed (All Subjects Set)
- Randomized
- Dosed (Safety Set)
- Randomized and dosed (FAS)
- Completed 6-Month Follow-up Visit
- Completed study
- Prematurely discontinued the study and the reasons for discontinuation

Subject disposition summary will be presented based on the All Subjects Set.

12.3.2.2 Demographics and Baseline Characteristics

Demographic, background (e.g., medical history), and baseline characteristics will be summarized. Protocol deviations/violations will be provided in a subject data listing only.

The following demographics and baseline characteristics will be summarized by treatment group for the FAS: sex, race, ethnicity, age, weight, height, BMI, country, AIS (A or B with or B without sacral pinprick preservation), and baseline UEMS score.

12.3.2.3 Prior and Concomitant Medications

Medications used in this study will be coded by the World Health Organization Drug Dictionary Enhanced (WHO-DDE) and will be categorized as follows:

- Prior medication: any medication that started prior to dosing with study drug, regardless of when it ended.
- Concomitant medication: medication continued or newly received at or after dosing of study drug through the end of the TE period.
- Post-treatment medication: medication continued or newly received after the TE period.

A given medication can be classified as a prior medication, a concomitant medication, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment. If a medication has a missing or partial missing start/end date or time and cannot be determined whether it was received prior to dosing with study drug, concomitantly, or beyond the TE period, it will be considered as prior, concomitant, and post-treatment.

Prior medications and concomitant medications will be summarized descriptively based on the FAS. Post-treatment medications will be listed for each subject.

12.3.2.4 Study Drug Exposure and Compliance

Study drug exposure will be presented in an individual data listing to indicate whether the study drug was administered.

12.3.3 Efficacy Analysis

Assessment of efficacy of VX-210 treatment is 1 of the primary objectives of this pivotal study. A hierarchical testing strategy will be used to preserve the overall 2-sided type I error rate at the 0.05 level. All efficacy endpoints will be analyzed based on the FAS.

12.3.3.1 Analysis of Primary Efficacy Variables

The primary efficacy endpoint is the change from baseline in UEMS at 6 months after treatment. The null hypothesis to be tested is that the mean change from baseline in UEMS at 6 months after treatment is the same for 9-mg dose of VX-210 and placebo.

The primary analysis will be based on a mixed-effects model for repeated measures (MMRM). The model will include the change from baseline in UEMS as the dependent variable; treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a

random effect, with adjustment for age and AIS grade (A versus B with sacral pinprick preservation versus B without sacral pinprick preservation) at baseline. In the model, visit will be treated as a class variable, and an unstructured covariance matrix will be assumed to model the within-subject variability. This model imposes no assumptions on the correlation structure and is considered robust. Denominator degrees of freedom for the F-test for fixed effects will be estimated using the Kenward-Roger approximation.[52] With a mixed-effects model based on restricted maximum likelihood estimation as the primary analysis and assuming that, conditional on fixed and random effects, data are missing at random, no imputation of missing data will be performed.

The primary result obtained from the model will be the estimated mean treatment effect at 6 months after treatment. The estimated mean treatment effect, a 95% CI, and a 2-sided *P* value will be provided. Furthermore, the treatment effect at each postbaseline visit, obtained from the model, will also be provided.

If there is a convergence problem due to the use of an unstructured covariance matrix, the unstructured covariance matrix will be replaced by a compound symmetric covariance matrix to model the within-subject errors.

[redacted]

12.3.3.2 Analysis of Secondary Efficacy Variables

For all secondary efficacy variables, the primary analysis will focus on the treatment effects at 6 months after treatment.

- SCIM III Self-Care subscore at 6 months after treatment: The analysis of this variable will be based on an analysis of covariance (ANCOVA) model, which will include the SCIM III Self-Care subscore at 6 months after treatment as the dependent variable, and treatment as a fixed effect, with adjustment for age and AIS grade (A versus B with sacral pinprick preservation versus B without sacral pinprick preservation) at baseline. If the SCIM III Self-Care subscore at 6 months after treatment is missing, the score at the Early Termination Visit will be carried forward for the analysis.
- CUE-T score at 6 months after treatment: The analysis of this variable will be similar to the analysis of the SCIM III Self-Care subscore.
- GRASSP Quantitative Prehension score at 6 months after treatment: The analysis of this variable will be similar to the analysis of the SCIM III Self-Care subscore.
- AIS grade conversion from baseline to 6 months after treatment: The response variable will be analyzed using the 2-sided Cochran-Mantel-Haenszel (CMH) test stratified by age (<30 versus ≥30 years of age) and AIS grade (A versus B with sacral pinprick preservation versus B without sacral pinprick preservation).
- Motor level change from baseline to 6 months after treatment: The analysis of this response variable will be similar to the analysis of the AIS grade conversion from baseline to 6 months after treatment.

[redacted]

12.3.3.4 Adjustment for Multiple Comparisons

The multiplicity adjustment will control the overall 2-sided type I error rate at 0.05 for testing 9-mg of VX-210 versus placebo for multiple endpoints.

The following multiplicity adjustment approach will be used to strongly control the overall 2-sided type I error rate at 0.05 for the primary endpoint and key secondary endpoints.

A hierarchical testing procedure will be used for the multiple endpoints at the 2-sided significance level $\alpha = 0.05$ as follows:

Step 1: The primary efficacy endpoint will be tested at significance level $\alpha = 0.05$.

Step 2: If VX-210 is statistically significant at $\alpha = 0.05$ from Step 1, the first key secondary efficacy endpoint will be tested at $\alpha = 0.05$.

At each step, the test for treatment effect will be considered statistically significant if the test meets the criteria for significance and all previous tests are also statistically significant. The first 2 layers of the testing hierarchy are as follows:

1. Change from baseline in UEMS at 6 months after treatment
2. SCIM III Self-Care subscore at 6 months after treatment

After the primary (change in UEMS) and first key secondary endpoint (SCIM III Self-Care) have met the level of significance for VX-210 compared to placebo, additional functional tests will be added to this hierarchy, with a test for treatment effect at each step that will be considered statistically significant only if the test is statistically significant and all previous

tests are also statistically significant. The hierarchy of endpoints after change in UEMS and SCIM III Self-Care subscore will be described in the SAP.

Note that the comparisons that cannot be performed formally due to hierarchical testing strategy will still be performed, and the corresponding P values will be considered descriptive.

12.3.4 Safety Analysis

All safety summaries will be based on the set of data associated with the TE period for subjects in the Safety Set.

The overall safety profile of VX-210 will be assessed in terms of the following safety and tolerability endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., hematology, serum chemistry, coagulation studies, and urinalysis)
- ECGs
- Vital signs

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

12.3.4.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs, or post-treatment AEs, defined as follows:

- Pretreatment AE: Any AE that started prior to dosing with study drug.
- TEAE: Any AE that developed or worsened at or after dosing of study drug through the end of the TE period.
- Post-treatment AE: Any AE that developed or worsened beyond the TE period.

For AEs with missing or partial missing start dates, if there is no clear evidence that the AEs started before or after study treatment, then the AEs will be classified as TEAEs.

AE summary tables will be presented for TEAEs only and will include the following:

- All TEAEs
- TEAEs by relationship
- TEAEs by maximal severity
- Serious TEAEs
- TEAEs leading to death

Summaries will be presented by MedDRA system organ class and preferred term using frequency counts and percentages (i.e., number and percentage of subjects with an event as well as total number of events). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be

counted once, only the maximum severity level will be presented in the severity summaries, and the worst/highest relationship level in the relationship summaries. An AE overview table will be provided. A separate table will summarize all TEAEs when each of them is considered unique, hereafter referred to as an AE count table. In addition, a listing containing individual subject AE data for all deaths and other serious and significant AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

12.3.4.2 Clinical Laboratory Assessments

The raw values and change from baseline values of the continuous laboratory parameters will be summarized in SI units by treatment group at each scheduled time point during the TE period.

The number and percentage of subjects with at least 1 potentially clinically significant (PCS) event during the TE period will be summarized by treatment group. The PCS criteria for clinical laboratory data will be provided in the SAP.

Immunogenicity results will be summarized in tables and listings.

Results of urinalysis and the serum pregnancy test will be listed in individual subject data listings only. In addition, a listing containing individual subject laboratory assessment values outside the reference ranges will be provided. Individual subject data listings will include data from scheduled and unscheduled time points.

12.3.4.3 Electrocardiograms

A summary of raw values and change from baseline values will be provided by treatment group at each scheduled time point during the TE period for the following standard 12-lead ECG measurements: PR, QT, QTc for heart rate (HR) interval (QTcF), QRS duration, and HR. In addition, the mean value at each visit will be plotted by treatment group for QTcF.

The number and percentage of subjects with at least 1 PCS event during the TE period will be summarized by treatment group. The PCS criteria for ECG data will be provided in the SAP.

12.3.4.4 Vital Signs

The raw values and change from baseline values during the TE period will be summarized by treatment group at each scheduled time point: systolic and diastolic blood pressure (mm Hg), body temperature (°C), HR (beats per minute [bpm]), and respiratory rate (breaths per minute).

The number and percentage of subjects with at least 1 PCS event during the TE period will be summarized by treatment group. The PCS criteria for vital signs data will be provided in the SAP.

12.3.4.5 Physical Examinations

Physical examination, including surgical site examination, results will be presented in individual subject data listings only. After screening, any clinically significant abnormal findings in physical examinations will be reported as AEs.

12.3.4.6 Other Safety Analysis

Not applicable.

12.3.5 Interim and IDMC Analyses

12.3.5.1 Interim Analyses

An interim analysis will be conducted when 33% of enrolled patients have completed the 6-Month Follow-up Visit. Based on the results of this interim analysis, the study may continue or stop for futility. The IDMC will conduct review of this interim analysis and make recommendation to the sponsor. If the study is considered unsuccessful at the time of the interim analysis, the study is to be terminated, study enrollment is to be stopped, and subjects are to be followed for safety reasons only.

Vertex will conduct the primary analysis for the study that includes safety, efficacy, and PK after all subjects receiving study drug have completed the 6-Month Follow-up Visit, or Early Termination Visit/Safety Follow-up Visit for subjects who prematurely terminate from the study before the 6-Month Follow-up Visit, and all data from these visits have been entered into the clinical study database, and the data have been cleaned and locked. If the study is considered unsuccessful at this primary analysis, the study is to be terminated and subjects are to be followed for safety reasons only. If the study is considered successful at this analysis, an updated analysis will be conducted by Vertex after all subjects receiving study drug have completed the 12-Month Follow-up Visit, or Early Termination Visit/Safety Follow-up Visit for subjects who prematurely terminate from the study before the 12-Month Follow-up Visit, and all data from these visits have been entered into the clinical study database, and the data have been cleaned and locked.

12.3.5.2 IDMC Analyses

An IDMC will be formed before study initiation. The IDMC's objectives and operational details will be defined in a separate document (IDMC charter), which will be finalized before the first subject is screened in the study. The IDMC will conduct regular planned safety reviews of study data as outlined in the IDMC Charter.

12.4 Clinical Pharmacology Analysis

12.4.1 Pharmacokinetic Analysis

The PK parameters of VX-210 will be determined using standard non-compartmental analysis and will be described using summary statistics.

Preliminary review and analyses of the drug concentrations may be done before database lock under the conditions of masked identifications of the subject concentrations. Unblinded PK analyses will be conducted after the database is cleaned and locked for the 6-month analysis.

If warranted, a population PK analysis of plasma concentration versus time data of VX-210 will be performed using the nonlinear mixed-effects modeling approach. Data permitting, the effect of demographic variables on PK parameters will be determined. The results from the population PK analysis will be included in a separate report.

[redacted]

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 preexisting 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, physical examinations, and vital signs, will be assessed and those deemed a 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
- 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 clinical status of the subject indicates a life-threatening AE.

13.1.1.3 Documentation of Adverse Events

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

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)

- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, the **latest** of:
  - 28 days after study drug treatment, or
  - The last study visit.

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

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

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and non-serious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed April 2017). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." The severity of an AE that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

Classification	Definition
Mild (Grade 1)	Mild level of discomfort and does not interfere with regular activities
Moderate (Grade 2)	Moderate level of discomfort and significantly interferes with regular activities
Severe (Grade 3)	Significant level of discomfort and prevents regular activities
Life-threatening (Grade 4)	Any adverse drug experience that places the subject, in the view of the investigator, at immediate risk of death

13.1.1.5 Adverse Event Causality

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

Table 13-2 Classifications for AE Causality

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

13.1.1.6 Study Drug Action Taken

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

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

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

13.1.1.7 Adverse Event Outcome

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

Table 13-4 Classifications for Outcome of an AE

Classification	Definition
Recovered/Resolved	Resolution of an AE with no residual signs or symptoms
Recovered/Resolved With Sequelae	Resolution of an AE with residual signs or symptoms

Table 13-4 Classifications for Outcome of an AE

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

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

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

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

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the subject signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure should 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) should not be considered to indicate an SAE.

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

13.1.2.2 Documentation of Serious Adverse Events

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

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

13.1.2.3 Reporting Serious Adverse Events

The investigator is responsible for notifying the sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. The Vertex Clinical Trial 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 Global Patient Safety via
Email: [redacted] (Preferred Choice)
Or via Fax: [redacted]
Contact Telephone: [redacted]

13.1.2.4 Expedited Reporting and Investigator Safety Letters

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

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

13.2 Administrative Requirements

13.2.1 Ethical Considerations

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

13.2.2 Subject Information and Informed Consent

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

13.2.3 Investigator Compliance

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

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

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

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

13.2.6 Record Retention

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

13.2.7 Study Termination

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

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

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

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

13.3 Data Quality Assurance

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

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure, validated web-based electronic data capture (EDC) application. Vertex will have read-only access to site-entered clinical data in the EDC application.

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

13.4 Monitoring

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

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

13.5 Electronic Data Capture

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

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

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

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

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

13.6 Publications and Clinical Study Report

[redacted]

13.6.2 Clinical Study Report

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

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16 PROTOCOL SIGNATURE PAGES

16.1 Sponsor Signature Page

Protocol #: VX15-210-101	Version #: 2.0	Version Date: 14 April 2017
Study Title: Phase 2b/3, Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of VX-210 in Subjects With Acute Traumatic Cervical Spinal Cord Injury		

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

[redacted]

Vertex Pharmaceuticals Incorporated [redacted]

16.2 Investigator Signature Page

Protocol #: VX15-210-101	Version #: 2.0	Version Date: 14 April 2017
Study Title: Phase 2b/3, Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of VX-210 in Subjects With Acute Traumatic Cervical Spinal Cord Injury		

I have read Protocol VX15-210-101, Version 2.0 and agree to conduct the study according to its terms. I understand that all information concerning VX-210 and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

_____
Printed Name

_____ _____
Signature Date