1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan
(Methods)

Protocol Number VX15-210-101 Version 2.0
(Final Analysis / Interim Analysis)

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

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4 INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis and interim analysis (IA) of study VX15-210-101 and is based on the

- approved clinical study protocol, 14 April 2017, Version 2.0
- approved eCRF, dated May 24 2018, Version 4.0

VX15-210-101 is a Phase 2b/3, double-blind, randomized, placebo-controlled multicenter study. This study will assess the efficacy and safety of VX-210 in subjects with acute traumatic cervical spinal cord injury.

This SAP (Methods) documents the interim and final efficacy and safety analysis and data presentation for VX15-210-101.

SAS® Version 9.4 Software (SAS Institute, Cary, North Carolina, USA) or higher will be used to generate all statistical outputs (tables, figures, listings and datasets).

The SAP (Methods) Version 1.0 was finalized and approved before the data cut for the interim analysis. The interim analysis methods specified in Section 10.1 of the SAP (Methods) Version 1.0 were implemented during the interim analysis. Any revisions to the approved SAP (Methods) Version 1.0 will be documented and approved prior to the final clinical database lock and treatment unblinding for the study.

Any changes made to the SAP (Methods) after the clinical data lock has occurred will be documented in the clinical study report for this study.

The analysis addressing the pharmacokinetic (PK) objective of the study will be described in the Clinical Pharmacology Analysis Plan (CPAP) which will be developed separately by the Clinical Pharmacology department at Vertex Pharmaceuticals Incorporated (Vertex). The independent data monitoring committee (IDMC) analyses are also described in a separate SAP.

5 STUDY OBJECTIVES

5.1 Primary Objective

Evaluation of the efficacy and safety of VX-210 treatment is the primary objective of the study.

5.2 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 activities of daily living (ADLs) and requirements for attendant care

[redacted]

6 STUDY ENDPOINTS

6.1 Primary Endpoint

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

6.2 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]

7 STUDY DESIGN

7.1 Overall Design

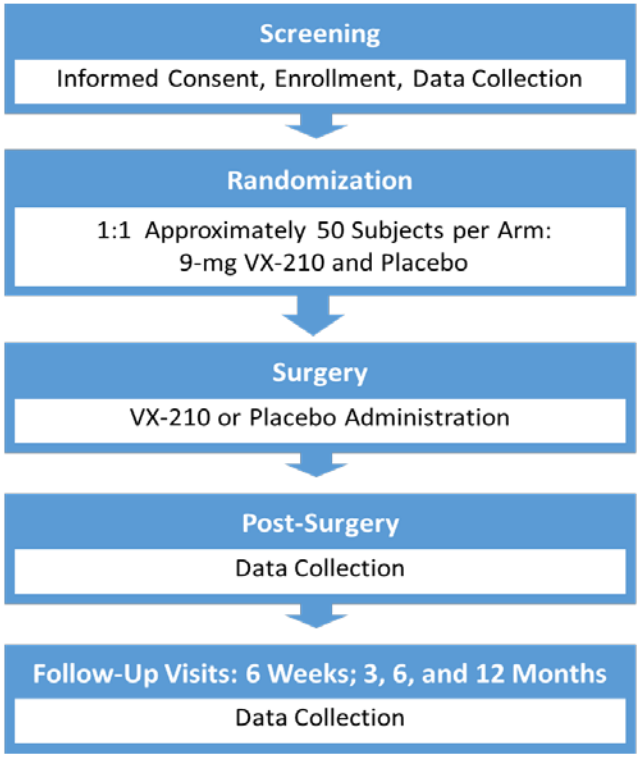
This is a multicenter, randomized, double-blind, placebo-controlled study to examine the efficacy and safety of VX-210 treatment. The study will be conducted at approximately 45 sites in the United States and Canada and will enroll approximately 100 male or female subjects 14 to 75 years of age (inclusive) 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.

A schematic of the study design is provided in Figure 7-1.

Figure 7-1 Schematic of Study Design



7.2 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., the SD was projected to be 3.8 for SCIM III Self-Care subscore. Table 7-1 presents the estimated power for detecting various

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 7-1 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 $\alpha = 0.05$.

7.3 Randomization

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.

7.4 Blinding and Unblinding

This will be a randomized double-blind study.

7.4.1 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 Study Execution Team (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.

7.4.2 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 of the protocol.

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.

8 ANALYSIS SETS

8.1 All Subjects Set

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.

8.2 Full Analysis Set

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.

8.3 Safety Set

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.

9 STATISTICAL ANALYSIS

9.1 General Considerations

The Schedule of Assessments is provided in Appendix A.

The precision standards for reporting safety and efficacy variables are provided in an internal Biometrics document that specifies the programming rules, including the precision for derived variables.

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

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

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

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:

Post baseline 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 / the last available visit (whichever is later) for subjects who do not have a Safety Follow-up Visit.

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

- In scheduled visit windows per specified visit windowing rules.
- In the derivation of baseline measurements
- In the derivation of maximum/minimum values and maximum/minimum changes from baseline values.
- In individual subject data listings as appropriate.

Visit window rules: The analysis visit windows for protocol-defined visits are provided in Appendix B.

Repeated observations within the same visit window:

- For all efficacy parameters, if there are multiple measurements within a visit window, the record at the scheduled visit will be used. If there are no measurements at the scheduled visit, then 1) the record closest to the target day will be used; or 2) if there are multiple records with the same distance to the target day, the latest record will be used.
- For all safety parameters, if there are multiple measurements within a visit window, then 1) the record closest to the target day will be used; or 2) if there are multiple records with the same distance to the target day, the latest record will be used.

Incomplete or missing data: If the SCIM III self-care subscore, CUE-T score, or GRASSP Quantitative Prehension score at 6 months after treatment is missing after the visit windows rules have been applied, the score at the early termination visit will be carried forward for the analysis.

Outliers: No formal statistical analyses will be performed to detect and/or remedy the presence of statistical outliers.

Unless otherwise specified, the analyses will be done by treatment group (VX-210 3 mg, VX-210 9 mg, Placebo), as some subjects have already been dosed with 3 mg using protocol version 1.0.

VX-210 3 mg will only be used in the following analyses:

1. Background characteristics (disposition, demographics/baseline characteristics, prior/ concomitant medications, etc.).
2. All safety analyses.

[redacted]

9.2 Background Characteristics

9.2.1 Subject Disposition

The number of subjects in the following categories will be summarized overall and by treatment group based on the All Subjects Set:

- All Subjects Set
- Randomized
- Dosed (Safety Set)
- Full Analysis Set (FAS)

The number and percentage (based on the Full Analysis Set) of subjects in each of the following disposition categories will be summarized overall and by treatment group:

- 6-Month Follow-up Visit Occurred
- Completed study
- Prematurely discontinued the study and the reasons for discontinuation

A listing will be provided for disposition, including the subjects who discontinued study with reasons for discontinuation. A randomization listing will be provided with subjects ordered by randomization date. A summary table for the randomization by stratification factors and by site will also be provided.

9.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized overall and by treatment group based on the Full Analysis Set.

Demographic data will include the following:

- Sex (female and male)
- Age at baseline (in years)
- Age group (<30 versus ≥30 years of age)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, not collected per local regulations, and Other)
- Country

Baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- AIS Grade (A or B with or B without sacral pinprick preservation)
- Baseline UEMS score (total, left and right)

All medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized using descriptive statistics by MedDRA system organ class (SOC) and preferred term (PT). Medical history will also be displayed in a subject listing.

9.2.3 Prior and Concomitant Medications

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

Prior medication: any medication that started before the dose date of study drug, regardless of when the medication ended.

Concomitant medication: medication continued or newly received on or after the dose date 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 may be classified as follows: prior, concomitant, post-treatment, both prior and concomitant, both concomitant and post-treatment, or prior, concomitant, and post-treatment.

If a medication has a completely missing or partially missing start/stop date and it cannot be determined whether it was taken before the dose date, concomitantly, or after the TE period, it will be classified as prior, concomitant, and post-treatment. Imputation rules for missing or partial medication start/stop dates are defined in Appendix C.

Prior medications and concomitant medications will be summarized descriptively by (1) preferred names; (2) anatomic class (ATC) level 1, ATC level 2, and preferred names based on the Full Analysis Set.

Summaries of medications will be based on the Full Analysis Set.

Post-treatment medications will be listed by subject.

9.2.4 Study Drug Exposure

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

9.2.5 Study Drug Compliance

Not applicable.

9.2.6 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. IPDs will be identified from the clinical database and/or site deviation log, and finalized prior to the database lock.

The protocol deviations that should be considered as potential IPDs may fall in, but are not limited to, the following categories:

- Safety
- Informed consent
- Eligibility and entry criteria
- Randomization
- Investigational medicinal product
- Study procedures and laboratory assessments

The protocol deviations that fall in these categories are categorized as IPDs only if they have the potential to significantly affect the completeness, accuracy, or reliability of the study data or to significantly affect a subject's rights, safety, or well-being.

IPDs will be provided in an individual subject data listing.

9.3 Efficacy Analysis

Assessment of efficacy of VX-210 treatment is one of the primary objectives of this pivotal study. All efficacy endpoints will be analyzed based on the FAS. All Efficacy data will be presented in listings based on the All Subjects Set.

The primary efficacy analysis in this study targets an estimand that would assess efficacy by using the change from baseline in the UEMS score at 6 months after treatment, focusing on the effect attributable to the initially randomized treatment.

Such an estimand targets the effect of the initially randomized treatment regimen, with consideration for the fact that enrolled subjects will also receive standard of care. With such

an estimand, all subjects in FAS with their primary efficacy endpoint data collected at 6 weeks, 3 months, 6 months, and 12 months after treatment are used to assess the targeted treatment effect. The primary efficacy analysis will be based on a mixed-effects model for repeated measures (MMRM), estimated using restricted maximum likelihood, treating the change from baseline in the UEMS score at 6 weeks, 3 months, 6 months, and 12 months after treatment as the dependent variable. If change from baseline in the UEMS score is missing after the visit windows rules have been applied, the missing value will be assumed to be Missing At Random (MAR) conditional on the observed data. With use of the MMRM model and the MAR assumption, no missing data will be explicitly imputed.

[redacted]

The primary result obtained from the primary efficacy analysis will be the estimated mean treatment effect at 6 months after treatment, and the estimated mean treatment effects at 6 weeks, 3 months, and 12 months after treatment, obtained from the model established, will also be provided.

[redacted]

9.3.1 Analysis of Primary Efficacy Variable(s)

9.3.1.1 Definition of Variable

Upper Extremity Motor Score (UEMS)

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. The range of the UEMS score is 0-50. The score collected in the CRF will be directly used in the analysis.

9.3.1.2 Primary Analysis

The UEMS score will be summarized at baseline, 6 weeks, 3 months, 6 months, and 12 months after treatment using the descriptive summary statistics by treatment group. The change from baseline in the UEMS score at 6 weeks, 3 months, 6 months, and 12 months after treatment will also be summarized descriptively by treatment group.

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

The primary efficacy analysis will be based on an MMRM model. The model will include the change from baseline in the UEMS score at 6 weeks, 3 months, 6 months, and 12 months after treatment 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 (only including A versus B with sacral pinprick preservation versus B without sacral pinprick preservation) at baseline. In the MMRM model, visit will be treated as a class variable, and an unstructured covariance matrix will be assumed to model the within-subject variability. Denominator degrees of freedom for the F-test for fixed effects will be estimated using the

Kenward-Roger approximation. If change from baseline in the UEMS score is missing after the visit windows rules have been applied, the missing value will be assumed to be MAR conditional on the observed data. With an MMRM model based on restricted maximum likelihood estimation as the primary efficacy analysis and under the MAR assumption, no imputation of missing data will be performed.

The primary result obtained from the primary efficacy analysis will be the estimated mean treatment effect (Least Squares [LS] means difference) at 6 months after treatment. The estimated mean treatment effect at 6 months after treatment, a 95% confidence interval (CI), and a 2-sided *P* value will be provided. Furthermore, the estimated mean treatment effects (with 95% CI) at 6 weeks, 3 months, and 12 months after treatment, obtained from the model established, will also be provided.

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

All UEMS data will be presented in a subject listing.

[redacted]

9.3.2 Analysis of Secondary Efficacy Variables

9.3.2.1 Secondary Analyses

Secondary efficacy endpoints will be summarized using descriptive summary statistics by treatment group and all post-baseline follow-up visits (AIS grade and motor level will also be summarized descriptively at baseline).

- SCIM III Self-Care subscore at 6 months after treatment: The range of the SCIM III Self-Care subscore is 0-20. The score collected in the CRF will be directly used in the analysis. The SCIM III Self-Care subscore at 6 weeks, 3 months, 6 months, and 12 months after treatment will be summarized descriptively by treatment group.
- CUE-T score at 6 months after treatment: The range of the CUE-T score is 0-128. The score collected in the CRF will be directly used in the analysis. The CUE-T score at 6 months after treatment will be summarized descriptively by treatment group.

- GRASSP Quantitative Prehension score at 6 months after treatment: The GRASSP Quantitative Prehension score will be derived as described in Appendix F. The range of the score is 0-60. The GRASSP Quantitative Prehension score at 6 months after treatment will be summarized descriptively by treatment group.
- AIS grade conversion from baseline at 6 months after treatment: An AIS responder is defined as a subject with improvement by ≥ 2 AIS grades (i.e., baseline AIS grade A changed to grade C, D, or E; baseline AIS grade B changed to D or E at 6 months after treatment). The AIS grade at baseline, 6 weeks, 3 months, 6 months, and 12 months after treatment will be summarized descriptively by treatment group. The AIS responder, defined as aforementioned, at 6 weeks, 3 months, 6 months, and 12 months after treatment will also be summarized descriptively by treatment group.
- Motor level change from baseline at 6 months after treatment: A motor level responder is defined as a subject with improvement by ≥ 2 motor levels on either side of the body (i.e., baseline level C4 changed to C6, C7, C8 on the left; or baseline level C5 changed to C7, C8… on the right and so on). A subject with a missing/not determined motor level on one side of the body for a given visit and an improvement of ⩾ 2 motor levels on the other side of the body at that visit will be classified as a responder for that visit; for all other cases in which one or both motor levels are missing/not determined at a given visit, the responder result at that visit will be noted as 'missing'. The motor level at baseline, 6 weeks, 3 months, 6 months, and 12 months after treatment will be summarized descriptively by treatment group. The motor level responder, defined as aforementioned, at 6 weeks, 3 months, 6 months, and 12 months after treatment will also be summarized descriptively by treatment group.

[redacted]

[redacted]

9.3.4 Multiplicity Adjustment

Not applicable.

9.4 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.

9.4.1 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 pre-treatment AEs/TEAEs/post-treatment AEs. Imputation rules for missing or partial AE start date are defined in the Appendix D.

AE summary tables will be presented for TEAEs only, overall and by treatment group, 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 listing containing individual subject AE data for all deaths and other serious AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

9.4.2 Clinical Laboratory

The raw values and change from baseline values of the continuous hematology, chemistry, and coagulation 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 overall and by treatment group. The PCS criteria are provided in Appendix E.

Immunogenicity analysis is out of the scope of this SAP.

Results of urinalysis and the serum pregnancy test will be listed in individual subject data listings only.

A listing of subjects with elevated liver function results (defined as any of the following: AST $\geq 3 \times$ ULN, ALT $\geq 3 \times$ ULN, ALP $\geq 1.5 \times$ ULN, or total bilirubin $\geq 2 \times$ ULN) during the TE period will be presented. For each subject in the listing, LFT assessments at all visits will be included.

In addition, listings 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.

9.4.3 Electrocardiogram

A summary of raw values and changes from baseline 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.

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

A listing containing individual subject ECG assessments will also be provided.

9.4.4 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 overall and by treatment group. The PCS criteria for vital signs data are provided in Appendix E.

A listing containing individual subject vital signs assessments will also be provided.

9.4.5 Physical Examination

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.

9.4.6 Other Safety Analysis

Not applicable

10 SUMMARY OF INTERIM AND IDMC ANALYSES

10.1 Interim Analysis

An interim analysis will be conducted when approximately 33% of enrolled subjects 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.

Based on the review of the data provided at the interim analysis meeting, the IDMC will make a recommendation regarding whether the study should continue or should stop for futility. The guideline for futility stopping will be that the 9-mg dose group improves in UEMS by less than approximately 1.19 points over placebo for the approximately 33% of subjects analyzed, under the assumed standard deviation (SD) of 6.

The IDMC will review the observed SD at the time of the interim analysis. If the SD deviates from the assumption, the futility guide is adjusted to be that the study will be stopped for futility if conditional power (under observed primary endpoint treatment effect size) is <10.6% or the observed primary endpoint treatment effect size is <1.19. The following table presents examples of the futility boundary with respect to different sizes of SD. The last column refers to the minimum observed primary endpoint effect size that is required to achieve statistical significance under the given size of SD at the final analysis.

Table 10-1 Guidelines for Futility Stopping

Standard Deviation	Futility Boundary	Conditional Power (Under	Minimum Required Observed

		Observed Effect Size)	Effect Size at Final Analysis
4	1.19	25.1%	1.7
6	1.19	10.6%	2.5
8	1.59	10.6%	3.3
10	1.98	10.6%	4.1

In all analyses supporting this interim analysis, only the first 43 randomized subjects will be used unless otherwise specified; this sub-population includes approximately 33% of enrolled subjects who are dosed with placebo or 9-mg of VX-210 and who will have completed the 6-month follow-up visit at the time of the interim analysis data cut.

10.1.1 Interim Background Characteristics

- **Subject disposition:**

  The number of subjects in the following categories will be summarized overall and by treatment group based on the All Subjects Set:

  - Randomized or dosed (All Subjects Set)
  - Randomized
  - Dosed (Safety Set)
  - Full Analysis Set

  The number and percentage (based on the Full Analysis Set) of subjects in each of the following disposition categories will be summarized overall and by treatment group:

  - 6-Month Follow-up Visit Occurred
  - Completed study
  - Prematurely discontinued the study and the reasons for discontinuation

  A listing will be provided for disposition, including the subjects who discontinued study with reasons for discontinuation.

- **Demographics and baseline characteristics:**

  Demographics and baseline characteristics will be summarized overall and by treatment group based on the Full Analysis Set.

  Demographic data will include the following:

  - Sex (female and male)
  - Age (in years)
  - Age group (<30 versus ⩾30 years of age)

- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, not collected per local regulations, and Other)
- Country

Baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- AIS Grade (A or B with or B without sacral pinprick preservation)
- Baseline UEMS score (total, left and right)

- **Prior and concomitant medications:**

  Medications used will be coded as described in section 9.2.3.

  A given medication may be classified as follows: prior, concomitant, post-treatment, both prior and concomitant, both concomitant and post-treatment, or prior, concomitant, and post-treatment.

  If a medication has a completely missing or partially missing start/stop date and it cannot be determined whether it was taken before the dose date, concomitantly, or after the TE period, it will be classified as prior, concomitant, and post-treatment. No imputation rules for missing or partial medication start/stop dates are applied.

  Prior medications and concomitant medications will be summarized descriptively using frequency tables by (1) by preferred names; (2) anatomic class (ATC) level 1, ATC level 2, and preferred names.

  Summaries of medications will be based on the Full Analysis Set.

  Post-treatment medications will be listed by subject.

10.1.2 Interim Efficacy Analysis

For the interim futility analysis data review meeting, the IDMC will be provided with statistical analyses of the following primary and secondary study endpoints and supportive data listings as appropriate. For all the interim efficacy analyses, no *P* value will be provided. All the efficacy endpoints aforementioned will be analyzed based on the FAS.

- Change from baseline in the UEMS score at 6 months after treatment**:** The UEMS score will be summarized at baseline, 6 weeks, 3 months, 6 months, and 12 months after treatment using the descriptive summary statistics by treatment group. The change from baseline in the UEMS score at 6 weeks, 3 months, 6 months, and 12 months after treatment will also be summarized descriptively by treatment group. The MMRM analysis of the change from baseline in the UEMS score at 6 months after

treatment in the interim analysis is similar to the MMRM analysis of the same variable in the primary analysis (see section 9.3.1.2) except for that no *P* value will be provided.

- SCIM III Self-Care subscore at 6 months after treatment**:** The SCIM III Self-Care subscore at 6 weeks, 3 months, 6 months, and 12 months after treatment will be summarized descriptively by treatment group. The analysis of the SCIM III self-care subscore at 6 months after treatment will be based on an 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 (only including 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 after the visit windows rules have been applied, the score at the early termination visit will be carried forward for the analysis. The estimated mean treatment effect (LS means difference) at 6 months after treatment and a 95% CI will be provided. No *P* value will be provided.
- CUE-T score at 6 months after treatment**:** The CUE-T score at 6 months after treatment will be summarized descriptively by treatment group. The ANCOVA analysis of the CUE-T score at 6 months after treatment is similar to the ANCOVA analysis of the SCIM III Self-Care subscore at 6 months after treatment in the interim analysis except for that the relevant endpoint here is the CUE-T score at 6 months after treatment.
- GRASSP Quantitative Prehension score at 6 months after treatment**:** The GRASSP Quantitative Prehension score at 6 months after treatment will be summarized descriptively by treatment group. The ANCOVA analysis of the GRASSP Quantitative Prehension score at 6 months after treatment is similar to the ANCOVA analysis of the SCIM III self-care subscore at 6 months after treatment in the interim analysis except for that the relevant endpoint here is the GRASSP Quantitative Prehension score at 6 months after treatment.
- AIS grade conversion from baseline at 6 months after treatment**:** The definition of an AIS responder is same as that in the primary analysis (see section 9.3.2.1). The AIS grade at baseline, 6 weeks, 3 months, 6 months, and 12 months after treatment will be summarized descriptively by treatment group. The AIS responder at 6 weeks, 3 months, 6 months, and 12 months after treatment will also be summarized descriptively by treatment group.
- Motor level change from baseline at 6 months after treatment**:** The definition of a motor level is same as that in the primary analysis (see section 9.3.2.1). The motor level at baseline, 6 weeks, 3 months, 6 months, and 12 months after treatment will be summarized descriptively by treatment group. The motor level responder at 6 weeks, 3 months, 6 months, and 12 months after treatment will also be summarized descriptively by treatment group.

10.1.3 Interim Safety Analysis

For reference, the following safety and supporting data will also be presented to the IDMC as unblinded tables and supportive data listings as appropriate. Analysis of safety/supporting data for the interim futility review meeting will be conducted in accordance with analyses for IDMC safety review meetings, and based on the Safety Set. The same general statistical consideration as described in section 9.1 of this SAP will be applied except for that no visit windows rules will be applied for the interim analysis.

- **Adverse events and/or serious adverse events (as available for all treatment arms):**

  For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs, or post-treatment AEs, defined as described in section 9.4.1.

  For AEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs started before or after study treatment, the AEs will be classified as pre-treatment AEs / TEAEs / post-treatment AEs. No imputation rules for missing or partial AE start date are applied.

  AE summary tables will be presented for TEAEs only, overall and by treatment group, 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 strongest relationship level in the relationship summaries. An AE overview table will be provided.

  In addition, a listing containing individual subject AE data for all deaths and other serious AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

- **Clinical laboratory values:**

  The raw values and change from baseline values of the continuous hematology, chemistry, and coagulation 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 overall and by treatment group. The PCS criteria are provided in Appendix E.

Results of urinalysis and the serum pregnancy test will be listed in individual subject data listings only.

In addition, listings 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.

- **Electrocardiogram outcomes:**

  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.

  The number and percentage of subjects with at least 1 PCS event during the TE period will be summarized overall and by treatment group. The PCS criteria are provided in Appendix E.

  A listing containing individual subject ECG assessments will also be provided.

- **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 overall and by treatment group. The PCS criteria are provided in Appendix E.

  A listing containing individual subject vital signs assessments will also be provided.

- **Physical examination results:**

  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.

- **Other Safety Analysis:**

  Not Applicable.

10.2 IDMC Safety Review Analyses

The Analyses for IDMC Safety Review meetings are described in the VX15-210-101 DMC Statistical Analysis Plan

11 REFERENCES

Not applicable.

12 LIST OF APPENDICES

Appendix A: Schedule of Assessments

The Schedule of Assessments is shown in Table 12-1.

Table 12-1 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.

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 of the protocol).

[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]

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.

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]

[q] 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.

Appendix B: Analysis Visit Windows for Safety and Efficacy Assessments

Table 12-2 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit	Target Study Day per the protocol	Analysis Visit Window (in study days)
Safety Assessment			
Hematology Serum Chemistry	6 Week Follow-Up	43	[8,67]
	3 Month Follow-Up	91	[68,365]
Efficacy Assessment			
ISNCSCI and SCIM III	6 Week Follow-Up	43	[8,67]
	3 Month Follow-Up	91	[68,136]
	6 Month Follow-Up	182	[137,273]
	12 Month Follow-Up	365	[274,450]
CUE-T and GRASSP Quantitative Prehension	6 Month Follow-Up	182	[8,365]

Special handling for Safety Follow-up, Surgery and Post-Surgery Visit:

Surgery, Post-Surgery and Safety Follow-up will use the nominal visit and will not follow the visit window rule.

Appendix C: Imputation Rules for Missing Prior/Concomitant Medication Dates

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date.
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last day of the month.
    b. If DAY and Month are both missing, use the last day of the year.
    c. If DAY, Month and year are all missing, assign 'continuing' status to stop date.

In summary, the prior, concomitant or post categorization of a medication is described below.

Table 12-3 Prior, Concomitant, and Post Categorization of a Medication

	Medication Stop Date		
Medication Start Date	**< First Dose Date of Study Drug**	**≥ First Dose Date and ≤ End Date of TE Period**	**> End Date of TE Period**
< First dose date of study drug	P	PC	PCA
≥ First dose date and ≤ End date of TE period	-	C	CA
> End date of TE period	-	-	A

A: Post; C: Concomitant; P: Prior

Appendix D: Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined below:

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date; otherwise, impute the AE start day as 1.
- Otherwise, impute the AE start day as 1.

Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date; otherwise, impute the AE start Month as January and the Day as 1.
- Otherwise, impute the AE start MONTH as January and the DAY as 1.

Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site with no imputation. Also compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date then the AE should be considered as a pretreatment AE. Otherwise, the AE will be considered as TEAE.

Appendix E: Criteria for Potentially Clinically Significant Events

Table 12-4 Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	PCS	Comments
Clinical Chemistry		
ALT	≤3xULN*(Not a PCS criterion) >3x - ≤ 5xULN >5x - ≤ 8xULN >3xULN >5xULN >8xULN	FDA DILI Guidance Jul 2009.
AST	≤3xULN*(Not a PCS criterion) >3x - ≤ 5xULN >5x - ≤ 8xULN >3xULN >5xULN >8xULN	FDA DILI Guidance Jul 2009.
ALT or AST	ALT>3xULN or AST>3xULN	Vertex LFT working group 2014
Alkaline Phosphatase	>1.5xULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>1.5x - ≤2xULN >2xULN	FDA DILI Guidance Jul 2009.
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009. To be counted within a same treatment phase, whatever the interval between measurements.
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009. To be counted within a same treatment phase, whatever the interval between measurements.
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	Vertex LFT working group 2014
CPK	>3x - ≤ 10xULN >10xULN	FDA criteria Feb 2005. Am J Cardiol April 2006.
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hypouricemia Hyperuricemia	 <120 µmol/L >408 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<85 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥150 mmol/L	

Table 12-4 Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	PCS	Comments
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.
Albumin	≤25 g/L	
Amylase	>2.0 - 5.0 x ULN >5.0 x ULN	Criteria based upon CTCAE
Lipase	>2.0 - 5.0 x ULN >5.0 x ULN	Criteria based upon CTCAE
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	<1.0 Giga/L >4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
RBC	≥6 Tera/L	
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

Table 12-5 Criteria for Potentially Clinically Significant ECGs

Parameter	PCS	Comments
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms	
QTc Borderline Prolonged* Additional	Absolute values (ms) Borderline: 431-450 ms (Male); 451-470 ms (Female) Prolonged: >450 ms (Male); >470 ms (Female) ≥500 ms Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula.
Coagulation		
aPPT	≥65 seconds	
PT	≥17 seconds	
INR	≥1.7	

Note: Based on CPMP 1997 guideline.

Table 12-6 Criteria for Potentially Clinically Significant Vital Signs

Parameter	PCS	Comments
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.

Appendix F: Details of Statistical Methodology

GRASSP Prehension Test scoring algorithm:

The total GRASSP score will be derived as the sum of the right total score and left total score collected in the CRF