1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX16-150-102 (Final Analysis)

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

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4 INTRODUCTION

This statistical analysis plan (SAP) for the final analysis is based on the approved clinical study protocol (CSP), dated 25 MAY 2018 for Version 5.0, 25 MAY 2018 for Version 5.1 NL, 25 MAY 2018 for Version 5.2 IT, 25 MAY 2018 for Version 5.3 DE, final electronic case report form (eCRF) completion guidelines, Version 2.0, dated 29 OCT 2018, and approved eCRF, Version 5.0, dated 19 OCT 2018.

Small fiber neuropathy is a distinct clinical condition caused by diseases affecting peripheral small nerve fibers (Aδ- and C-fibers). Common symptoms include burning pain in the feet and evoked pain (e.g., pressure and touch allodynia). Diagnosis is defined as possible, probable, and definite based on the combination of symptoms, signs, evidence of large sensory nerve fiber function integrity by nerve conduction studies (NCS) and abnormal skin biopsy or quantitative sensory testing. By inhibiting $Na_v1.8$ in the peripheral nerve fibers, VX-150 has the potential to treat pain caused by hyperexcitability of the damaged or diseased nerves.

Study VX16-150-102 is a proof-of-concept study that will evaluate the efficacy, tolerability, PK and safety of VX-150 in the treatment of neuropathic pain in subjects with small fiber neuropathy.

This SAP (Methods) documents the planned final statistical analysis of efficacy and safety endpoints defined in the study protocol of VX16-150-102 and provide additional details and clarifications.

The Vertex Biometrics Department will perform the final statistical analysis of the efficacy and safety data; 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) for the final analysis will be finalized and approved before the database lock for the final analysis. Any changes made to the SAP after the clinical database 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).

5 STUDY OBJECTIVES

5.1 Primary Objective

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

5.2 Secondary Objectives

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

6 STUDY ENDPOINTS

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoint

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

6.1.2 Secondary Efficacy Endpoints

- Proportion of subjects with ≥30% reduction in the weekly average of daily pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6
- Proportion of subjects with ≥50% reduction in the weekly average of daily pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6
- Change from baseline in the Daily Sleep Interference Scale (DSIS) at Week 6
- Proportion of subjects categorized as improved at Week 6 on the patient global impression of change (PGIC) assessment
- Change from baseline in pain intensity on the 11-point NRS, as reported at study visits, at Week 6

[redacted]

6.2 Safety Endpoints

- Safety and tolerability based on the Columbia Suicide Severity Rating Scale (C-SSRS), incidence and type of AEs, changes from baseline in clinically significant laboratory test results, vital signs, and ECGs at each visit

7 STUDY DESIGN

7.1 Overall Design

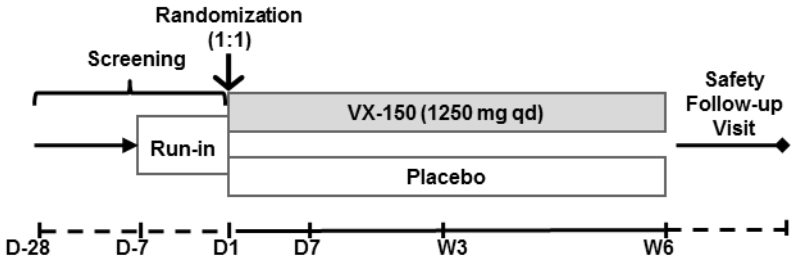
This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter study (Figure 7-1). Up to approximately 114 subjects with small fiber neuropathy will be randomized 1:1 to VX-150 or placebo.

This study will include:

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

- A 28-day Safety Follow-up

Figure 7-1 VX16-150-102 Study Design



D: Day; qd: daily; W: Week

7.2 Sample Size and Power

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

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

Table 7-2 Power for the 95% Confidence Intervals for Within- and Between-group Changes

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

7.3 Randomization

Up to approximately 114 subjects with small fiber neuropathy will be randomized 1:1 to VX-150 or placebo. Randomization will be stratified by sex and diagnosis of diabetes. Subjects with diabetes will not exceed approximately 60% of the total number of subjects. Subjects with diabetes and HbA1c ≥8% and <11% at screening will not exceed approximately 20% of the total number of subjects.

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

7.4 Blinding and Unblinding

This will be a double-blind study.

7.4.1 Blinding

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

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the subject and the fetus in the event of a pregnancy
- An unblinded pharmacist at the contract research organization (CRO) for dispensing study drug
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy serious adverse event (SAE) processing and reporting regulations
- External vendor (unblinded) statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IXRS Management for IXRS oversight and system administration
- Vertex Clinical Supply Chain
- The bioanalytical laboratory/vendor personnel managed by Vertex Bioanalysis

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

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

In addition, a Vertex Clinical Pharmacologist will be partially unblinded to help in management of the PK workspace and ensure that only the blinded PK data set is being provided for preliminary analysis. This individual, however, will not be a member of the

SET, and will not interact with the CRU or study personnel. Masked IDs will be used for these analyses.

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.

8 ANALYSIS SETS

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

8.1 All Subjects Set

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

8.2 Full Analysis Set

The Full Analysis Set (FAS) is defined as all randomized subjects who have received at least 1 dose of study drug. The FAS is to be used in efficacy analyses in which subjects will be analyzed according to their randomized treatment group and not to the treatment they actually received.

8.3 Safety Set

The Safety Set is defined as all subjects who have received at least 1 dose of study drug. The Safety Set is to be used for all safety analyses in which subjects will be analyzed according to the treatment they received and not according to their randomized treatment group.

9 STATISTICAL ANALYSIS

9.1 General Considerations

The Schedule of Assessments is provided in Section 3 of CSP. 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, including those derived, for subjects who were randomized or received at least 1 dose of study drug, i.e. All Subjects Set, will be presented in individual subject data listings as described.

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

Categorical variables will be summarized using counts and percentages.

Baseline value for the NRS via daily diary and the DSIS will be defined as the average score of at least 4 nonmissing scores from Day -7 to Day -1. For all other variables baseline will be defined as the most recent nonmissing measurement collected before the initial administration of study drug unless specified otherwise.

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

Treatment-emergent (TE) Period will be defined as the time from dosing with study drug until the following time point:

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

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/last on-treatment measurements.
- In the derivation of maximum/minimum on-treatment values and maximum/minimum change from baseline values for safety analyses.
- In individual subject data listings as appropriate.

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

Incomplete/missing data will not be imputed, unless otherwise specified.

Outliers: No formal statistical analyses will be performed to detect or remedy the presence of statistical outliers, unless specified otherwise.

Multiplicity: No multiplicity adjustment will be performed for hypothesis testing.

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:

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

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

- Completed treatment
- Prematurely discontinued the treatment and the reason for discontinuation
- Completed study (i.e., completed Safety Follow-up Visit)
- Prematurely discontinued the study and the reason for discontinuation

A listing will be provided for subjects who discontinued treatment or who discontinued study with reasons for discontinuation. A randomization listing of subjects will be provided.

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

9.2.2 Demographics and Baseline Characteristics

Demographics, medical history and baseline characteristics will be summarized overall and by treatment group based on the FAS.

Demographic data will include the following:

- Age (in years)
- Sex (male, female)
- 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, Other and Multiracial (if more than 2 races reported from a subject))

Baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

- Diagnosis of diabetes (Yes, No)

Disease characteristics will include the following:

- Pain intensity at baseline as recorded on the NRS
- Daily sleep interference at baseline as recorded on the DSIS

Small fiber neuropathy history will include the following:

- Distribution of the symptoms (stocking/glove distribution, non-length dependent)
- The small fiber neuropathy symptoms have been present for >= 3 months (Yes, No)
- Quality of the small fiber neuropathy symptoms (burning, sharp stabbing, throbbing, cold sensation, itch, loss of sensation and other)
- Autonomic features associated with the small fiber neuropathy (Yes, No)

Medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT).

9.2.3 Prior and Concomitant Medications

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

1. Prior medication: Medication that started before the first dose of study drug, regardless of when dosing of the medication ended.
2. Concomitant medication: Medication received at or after the first dose of study drug, medication that was received before initial dosing and continued after initial dosing of study drug, or medication with missing stop date.

Medication that started before the first dose of study drug and continued after the first dose of study drug will be summarized as prior medication and separately as concomitant medication.

If a medication has a completely missing or partially missing start/stop date and it cannot be determined whether it was taken before the first dose date or concomitantly, it will be classified as prior and concomitant.

Details for imputing missing or partial start and/or stop dates of medication are described in Appendix B.

9.2.4 Study Drug Exposure and Study Drug Compliance

Study drug exposure and study drug compliance summaries will be based on the FAS.

Duration of study drug exposure is defined as follows: last dose date – first dose date + 1 day, regardless of any interruption in dosing between the first and the last dose. Duration of study drug exposure expressed in weeks will be summarized by means of descriptive summary statistics and also into the following categories: ≤1 weeks, >1 and ≤3 weeks, >3 and ≤6.5 weeks, and >6.5 weeks.

Dosing compliance rate will be calculated as following:

100× [(total number of tablets dispensed) – (total number of tablets returned)] / (total number of tablets planned to be taken per day × duration of study drug exposure in days).

The dosing compliance rate will be summarized descriptively and into the categories of <80%, and ≥80%.

9.2.5 Important Protocol Deviations

Important protocol deviation (IPD) is a subset of protocol deviations (any change, divergence, or departure from the study design or procedures defined in the protocol) that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subjects' rights, safety or well-being. IPDs will be identified from the clinical database and/or site deviation log.

A list of categories of IPDs identified for this study is presented in Appendix E.

All IPDs will be summarized descriptively by treatment group and presented in an individual subject data listing.

9.3 Efficacy Analysis

Unless otherwise defined, all efficacy analyses described in this section will be based on the FAS. Subjects will be analyzed according to their randomized treatment assignment.

9.3.1 Analysis of Primary Efficacy Variable

9.3.1.1 Definition of Primary Efficacy Variable

The primary efficacy endpoint is the change from baseline in the weekly average of daily pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6. The weekly average of daily pain intensity will be calculated by averaging the nonmissing daily pain intensity scores in each week. If the count of nonmissing daily pain intensity scores is less than 4 within a week, the weekly average of daily pain intensity will be set to missing.

9.3.1.2 Primary Analysis

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

The model will include the change from study baseline at each week in the weekly average of daily pain intensity score as the dependent variable; treatment, sex, diagnosis of diabetes, week, and treatment-by-week interaction as fixed effects and baseline pain intensity score as a covariate. The model will be estimated using restricted maximum likelihood. The denominator degrees of freedom for the F-test for fixed effects will be estimated using the Kenward-Roger approximation. In the model, an unstructured covariance matrix will be assumed to model the within-subject variability. 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.

Conditional on the observed data and covariates, missing data will be assumed to be missing at random; consequently, no imputation of missing data will be performed.

The post-baseline raw values and the change from baseline at each week will be summarized descriptively (n, mean, SD, SE, median, minimum, and maximum).

The adjusted mean (SE), corresponding 95% 2-sided confidence interval (CI) and 2-sided *P* value for VX-150 treatment group in change from study baseline in weekly average of daily NRS at Week 6 will be provided. The CI will first be used to facilitate the comparison with 0; this will be followed by a comparison with 0.8. Furthermore, the adjusted mean (SE) and corresponding 95% CI for the treatment difference between VX-150 and placebo at Week 6 will be provided.

In addition, adjusted means (SE) and 95% CIs for all within-group treatment and between-group treatment comparisons at other weeks will also be provided.

9.3.2 Analysis of Secondary Efficacy Variables

9.3.2.1 Definition of Secondary Efficacy Variables

Proportion of subjects with ≥30%, ≥50% reduction in the weekly average of daily pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6: The percentage reduction in the weekly average of daily pain intensity will be calculated as following:

100 × (daily pain intensity score at baseline −the weekly average of daily pain intensity score at Week 6) / daily pain intensity score at baseline.

Change from baseline in the DSIS at Week 6: The change from baseline in the DSIS at Week 6 is the change from baseline in the weekly average of daily sleep interference score on the DSIS, as reported in the daily diary at Week 6. The weekly average of DSIS will be calculated by averaging the nonmissing daily sleep interference scores in each week. If the count of nonmissing daily sleep interference scores is less than 4 in a week, the weekly average of daily sleep interference on the DSIS will be set to missing.

Proportion of subjects categorized as improved at Week 6 on the PGIC assessment: The assessment consists of a single item on a 7-point scale from 1 (very much improved) to 7 (very much worse). Subjects will be categorized as following:

- 1 - 2 reported on the PGIC assessment will be categorized as “improved”;
- 3 - 4 reported on the PGIC assessment will be categorized as “no change”;
- 5 - 7 reported on the PGIC assessment will be categorized as “worse”.

Change from baseline in pain intensity on the 11-point NRS, as reported at study visits, at Week 6: Change from baseline in pain intensity will be calculated at each post-baseline visit (Day 7, Week 3 and Week 6) following the general definition of the baseline and change from baseline in Section 9.1.

9.3.2.2 Secondary Analyses

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

Proportion of subjects with ≥50% reduction in the weekly average of daily pain intensity on the 11-point NRS, as reported in the daily diary, at Week 6: Analysis of this variable will be the same as described for proportion of subjects with ≥30% reduction.

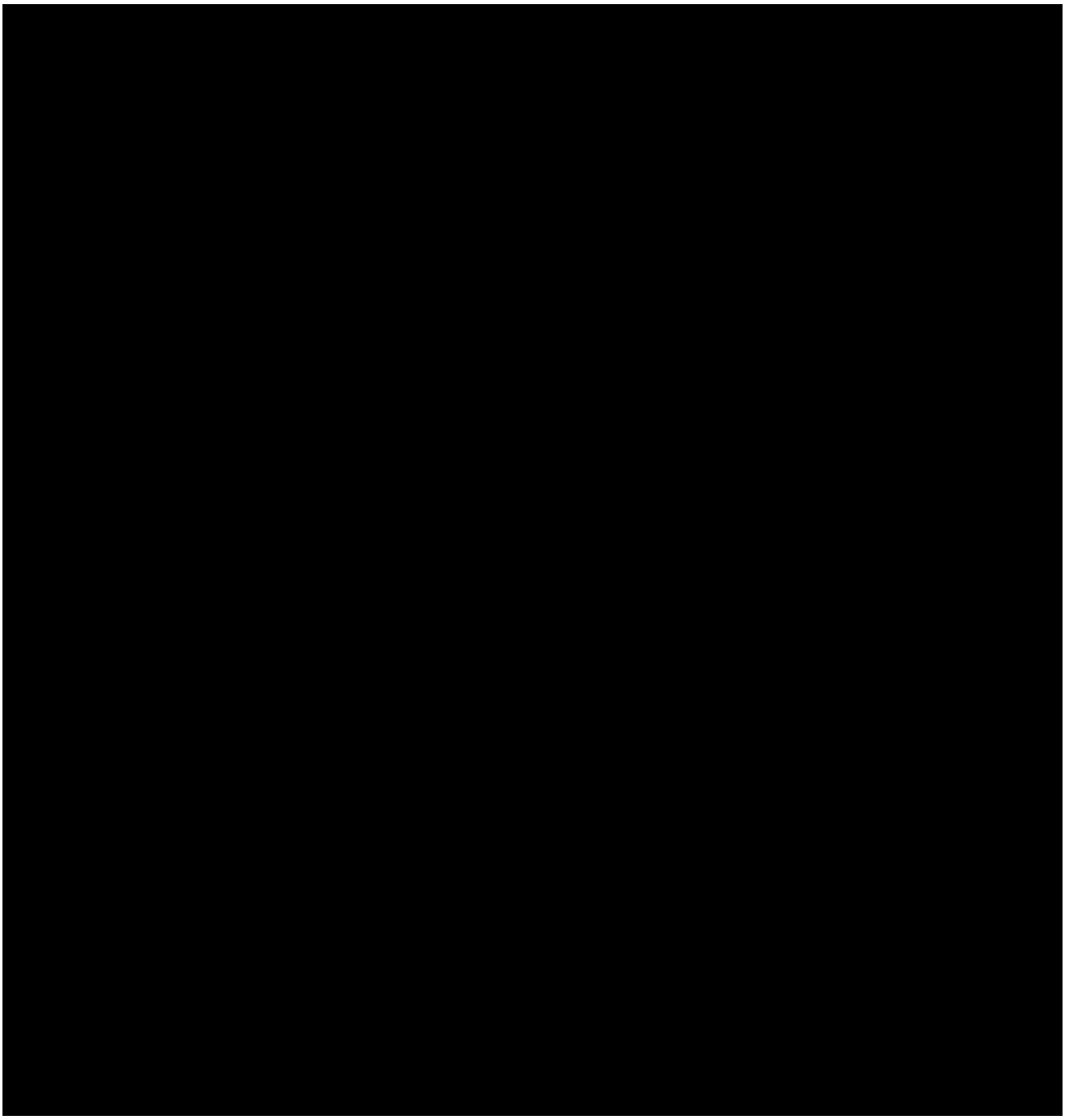
In addition, the proportion of subjects with ≥70% reduction in the weekly average of daily pain intensity at Week 6 will also be analyzed in the same way as described for the proportion of subjects with ≥30% reduction.

Change from baseline in the DSIS at Week 6: Analysis of this variable will be based on an MMRM similar to the analysis of the primary efficacy variable. Weekly average of daily DSIS score at each week will be included in the model as the dependent variable.

Proportion of subjects categorized as improved at Week 6 on the PGIC assessment: This variable will be evaluated using descriptive statistics by treatment group.

Change from baseline in pain intensity on the 11-point NRS, as reported at study visits, at Week 6: Analysis of this variable will be based on an MMRM similar to the analysis of the primary efficacy variable. The change from baseline in NRS at each post-baseline visit (Day 7, Week 3 and Week 6) will be included in the model as the dependent variable.

[redacted]



9.4 Safety Analysis

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

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values
- ECG outcomes

- Vital signs
- C-SSRS

Safety analyses will be based on the Safety Set.

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

Safety analyses will be based on the Safety Set and subjects will be analyzed according to the treatment they actually received. In an unexpected scenario that a subject may receive more than one treatment in the study, the following algorithm will be used to define subject's actual treatment: for any dosed subjects, the actual treatment is defined as VX-150 if the subject received any VX-150 treatment, regardless of the randomized treatment assignment. Otherwise, the actual treatment is defined as placebo only if the subject receives placebo at all visits in the study.

9.4.1 Adverse Events

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

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

Treatment-emergent AEs are defined as AEs that were reported or worsened on or after the first dose date of study drug through the end of the TE period.

Details for imputing missing or partial start dates of adverse events are described in Appendix C.

Only TEAEs will be summarized in tables. All summaries of TEAEs will be presented by the severity of the AE and relationship to the study drug. Some rules that will apply to the summarization of AEs are (1) a subject with multiple occurrences of the same AE or a continuing AE will only be counted once; (2) only the maximum severity level will be presented in the severity summary; and (3) only the strongest relationship level will be presented in the relationship summary. An AE with relationship missing is counted as related AE.

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

9.4.2 Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using International System of Units. The raw values and change from baseline values for the continuous hematology, clinical chemistry will be summarized by treatment group at each scheduled visit. The threshold value criteria for hematology and clinical chemistry laboratory tests are provided in Appendix D. The number and percentage of subjects with at least 1 hematology and clinical chemistry laboratory measurement meeting the threshold value criteria will be summarized

by treatment group at each scheduled visit. Coagulation results will be summarized by treatment group at each scheduled visit. The number and percentage of subjects with abnormal coagulation values at each scheduled time point will be summarized.

A listing containing individual subject hematology and clinical chemistry laboratory measurements meeting the threshold value criteria at any visit will be provided. For each subject in the listing, laboratory measurements at all visits will be included. This listing will include data from scheduled and unscheduled time points. Abnormal coagulation and urinalysis results also will be listed separately. For each subject in the listing, coagulation and urinalysis results at all visits will be included. Results of the urine/serum pregnancy test will be presented in individual subject data listings only.

Clinically significant abnormal laboratory findings will be reported as AEs.

9.4.3 Electrocardiogram

A summary of raw values and change from baseline values will be provided by treatment at each scheduled visit during the TE period for the following standard 12-lead ECG measurements: PR, QT, QRS, QTcF [$QTcF = QT/RR^{0.33}$], and HR. In addition, the number and percentage of subjects by maximum on-treatment value of QT/QTcF intervals, categorized as ≤450 msec, >450 msec and ≤480 msec, >480 msec and ≤500 msec, and >500 msec, as well as maximum on-treatment change from baseline value of QT/QTcF intervals, categorized as ≤0 msec, >0 and ≤30 msec, >30 and ≤60 msec, and >60 msec, will be provided.

The threshold value criteria for ECG data are provided in Appendix D. A listing containing individual subject measurements meeting the threshold value criteria at any visit will be provided. For each subject in the listing, ECG measurements at all visits will be included.

Clinically significant ECG abnormalities occurring during the study through the Safety Follow-up Visit will be recorded as AEs.

9.4.4 Vital Signs

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

The threshold value criteria for vital signs data are provided in Appendix D. A listing containing individual subject measurements meeting the threshold value criteria at any visit will be provided. For each subject in the listing, vital signs at all visits will be included.

Clinically significant abnormal findings in vital signs will be reported as AEs.

9.4.5 C-SSRS

The responses to the first two questions in the C-SSRS will be summarized by treatment at baseline and at each scheduled visit:

- Wish to be dead
- Non-specific active suicidal thoughts

Subjects with "yes" response to either of the first two questions at baseline and at any scheduled visit will be listed separately. For each subject in the listing, responses to all questions in the C-SSRS at all visits will be included.

9.4.6 Physical Examination

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

9.4.7 Neurological Examination

Neurological Examination results will be presented in a data listing only.

9.4.8 Bedside Sensory Testing Kit

Bedside Sensory Testing Kit results will be presented in a data listing only.

10 SUMMARY OF INTERIM AND IDMC ANALYSES

Not applicable.

11 REFERENCES

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12 LIST OF APPENDICES

Appendix A: Analysis Visit Windows for Safety and Efficacy Assessments

Table 12-1 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[1]	Target Study Day per the protocol	Analysis Visit Window (in study days)
Safety Assessment			
Hematology Serum Chemistry	Baseline	1	[Screening visit, Pre-dose Day 1]
	Week 3	22	[1*, 32]
	Week 6	43	[33, 57]
	Safety Follow-up Visit	N/A	Nominal
Coagulation	Baseline	N/A	[Screening visit, Pre-dose Day 1]
	Week 6	43	[1*, 57]
	Safety Follow-up Visit	N/A	Nominal
Standard 12-Lead ECG	Baseline	1	[Screening visit, Pre-dose Day 1]
	Day 7	7	[1*, 57]
	Safety Follow-up Visit	N/A	Nominal
Vital Sign	Baseline	1	1
	Day 7	7	[2, 14]
	Week 3	22	[15, 32]
	Week 6	43	[33, 57]
	Safety Follow-up Visit	N/A	Nominal
C-SSRS	Baseline	1	[-1, 1]
	Day 7	7	[2, 14]
	Week 3	22	[15, 32]
	Week 6	43	[33, 57]
	Safety Follow-up Visit	N/A	Nominal

Table 12-1 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[1]	Target Study Day per the protocol	Analysis Visit Window (in study days)
Efficacy Assessment			
NRS via daily diary DSIS via daily diary	Baseline	N/A	[-7, -1][2]
	Week 1	N/A	[1*, 7]
	Week 2	N/A	[8, 14]
	Week 3	N/A	[15, 21]
	Week 4	N/A	[22, 28]
	Week 5	N/A	[29, 35]
	Week 6	N/A	[36, 42]
NRS reported at study visits PGIC [redacted]	Baseline	1	Before first dose of study drug
[redacted]	Day 7	7	[1*, 14]
	Week 3	22	[15, 32]
	Week 6	43	[33, 57]
	Safety Follow-up Visit	N/A	Follow the individual visit window to be mapped to individual visits if measured before / on Day 57 or remain as SFU if otherwise.

[redacted]

1* only include day 1 post-dose measurements.
[1] Visit name for analysis purpose is used to report data in tables and figures.
[2] Only include 7 day measurements before the randomization day.

Notes:
The analysis visit windows will be applied using the following rules for both scheduled and unscheduled visits:

1. If no numerical measurement is available within a visit window, the measurement will be considered missing for the visit.

2. If there is more than 1 numerical measurement available within the same visit window, use the following rules:
   a. a. For **efficacy** assessments: if there are multiple measurements within a visit window,
      i. The measurement closest to the target day will be used; or
      ii. If there are multiple measurements within the same distance from the target day, the latest measurement will be used.
   b. For **safety** assessments: if there are multiple measurements within a visit window,
      i. The measurement closest to the target day will be used; or
      ii. If there are multiple measurements within the same distance from the target day, the latest measurement will be used.

3. When define efficacy and safety at baseline, refer to the generic baseline definition in Section 9.1. If the first dose time is missing, baseline will be defined as the most recent nonmissing measurement collected before the date of the first dose of study drug. For vital sign, there is no time collected and Day 1 will be baseline. For CSSR-S, baseline will be defined as the most recent nonmissing measurement collected before/on Day 1.

4. If the first dose time is missing, use the first dose date to determine post-dose measurements.

Appendix B: 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 and/or concomitant categorization of a medication is described below.

Table 12-2 Prior and/or Concomitant 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**
< First dose date of study drug	P	PC
≥ First dose date and ≤ End date of TE period	-	C

C: Concomitant; P: Prior

Appendix C: 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, or TEAE.

If Day and Month of AE start date are missing:

If AE start year is the same as 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, or TEAE.

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 D: Threshold Value Criteria

Table 12-3 Threshold Value Criteria for Laboratory Tests

Parameter		Comments
Clinical Chemistry		
ALT	≤3xULN*(Not a PCS criterion) >3x to ≤ 5xULN >5x to ≤ 8xULN >3xULN >5xULN >8xULN	FDA DILI Guidance Jul 2009.
AST	≤3xULN*(Not a PCS criterion) >3x to ≤ 5xULN >5x to ≤ 8xULN >3xULN >5xULN >8xULN	FDA DILI Guidance Jul 2009.
ALT or AST	ALT>3xULN or AST>3xULN	Vertex LFT working group 2014. To be counted within the same treatment period.
Alkaline Phosphatase	>1.5xULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>1.5x to ≤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 period.
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009. To be counted within a same treatment period.
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	Vertex LFT working group 2014. To be counted within the same treatment period.
CK	>3x to ≤ 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.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<85 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥150 mmol/L	

Table 12-3 Threshold Value Criteria for Laboratory Tests

Parameter		Comments
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Glucose		
Hypoglycaemia	<2.2 mmol/L	CTCAE criteria.
Hyperglycaemia	>13.9 mmol/L (fasted)	CTCAE criteria.
Albumin	≤25 g/L	
Thyrotropin	< LLN > ULN	
Cholesterol	≥20% increase from baseline	D. M. Hegsted and Robert J. Nicolos, 1987 Demacker PN et al., 1982.
Triglycerides	≥20% absolute change from baseline	D. M. Hegsted and Robert J. Nicolos, 1987 Demacker PN et al., 1982.
Low-density lipoprotein-direct	≥20% increase from baseline	D. M. Hegsted and Robert J. Nicolos, 1987 Demacker PN et al., 1982.
High-density lipoprotein	≥ 20% decrease from baseline	D. M. Hegsted and Robert J. Nicolos, 1987 Demacker PN et al., 1982.
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	>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 12-4 Threshold Value Criteria for ECGs

Parameter		Comments
HR	≤50 bpm and decrease from baseline ≥10 bpm ≥120 bpm and increase from baseline ≥10 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.

Note: Based on CPMP 1997 guideline.

Table 12-5 Threshold Value Criteria for 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	≤90 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.
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA criteria Feb 2007.

Appendix E: Important Protocol Deviation Categories

- Informed Consent
- Study Conduct/ Procedures
- Investigational Product
- Safety
- Other