1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX18-150-104 (Final Analysis)

A Phase 2B Randomized, Double-blind, Placebo-controlled, Dose-ranging, Parallel-design Study of the Efficacy and Safety of VX-150 for Acute Pain Following Bunionectomy

Author of SAP: [redacted]

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Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, Massachusetts 02210-1862

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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 26 September 2018 for Version 2.0, approved eCRF, Version 3.0, dated 31 January and final electronic case report form (eCRF) completion guidelines, Version 2.0, dated 11 February.

Study VX18-150-104 is a Phase 2 dose-ranging study which was designed to help inform dose selection for Phase 3 studies in acute pain. This SAP (Methods) documents the planned final statistical analysis of efficacy and safety endpoints defined in the study protocol of VX18-150-104 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 and R Version 3.5.0 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 dose-response relationship of VX-150 in treating acute pain following bunionectomy

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 (M5)

6 STUDY ENDPOINTS

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoint

Time-weighted sum of the pain intensity difference between VX-150 versus placebo as recorded on a Numeric Pain Rating Scale (NPRS) 0 to 24 hours (SPID24) after the first dose

6.1.2 Secondary Efficacy Endpoints

- Time-weighted sum of the pain intensity difference between VX-150 versus placebo as recorded on an NPRS 0 to 48 hours (SPID48) after the first dose

- Proportions of subjects with at least 30%, 50%, or 70% reduction in NPRS at 24 hours after the first dose of VX-150 versus placebo
- Time to onset of "confirmed perceptible pain relief" and "meaningful pain relief" after the first dose of VX-150 versus placebo

[redacted]

6.2 Safety Endpoints

- Safety and tolerability based on the incidence and type of adverse events (AEs), changes from baseline in clinically significant laboratory test results, and vital signs at designated visits

7 STUDY DESIGN

7.1 Overall Design

This is a Phase 2B randomized, double-blind, placebo-controlled, dose ranging, 6-arm, parallel-design study. Subjects will receive a primary unilateral first metatarsal bunionectomy repair on Day -1 (Figure 7-1). A continuous popliteal sciatic block infusion (0.2% ropivacaine) will be started after surgery and will be removed between 3AM and 5AM on Day 1. After removal of the popliteal sciatic block, a subject can be randomized once the subject requests the first dose of study drug for pain relief, and the subject's pain is ≥4 on the NPRS and is moderate or severe on the VRS (Verbal Categorical Rating Scale). If a subject does not meet the NPRS and VRS criteria within 9 hours of removal of the popliteal sciatic block, the subject will not be eligible to enroll in the study.

A total of approximately 242 subjects will be randomized 2:2:2:2:1:2 to 6 treatment arms, evaluating a range of 5 VX-150 dose levels as shown in Table 7-1.

Table 7-1 VX-150 Doses by Treatment Arm

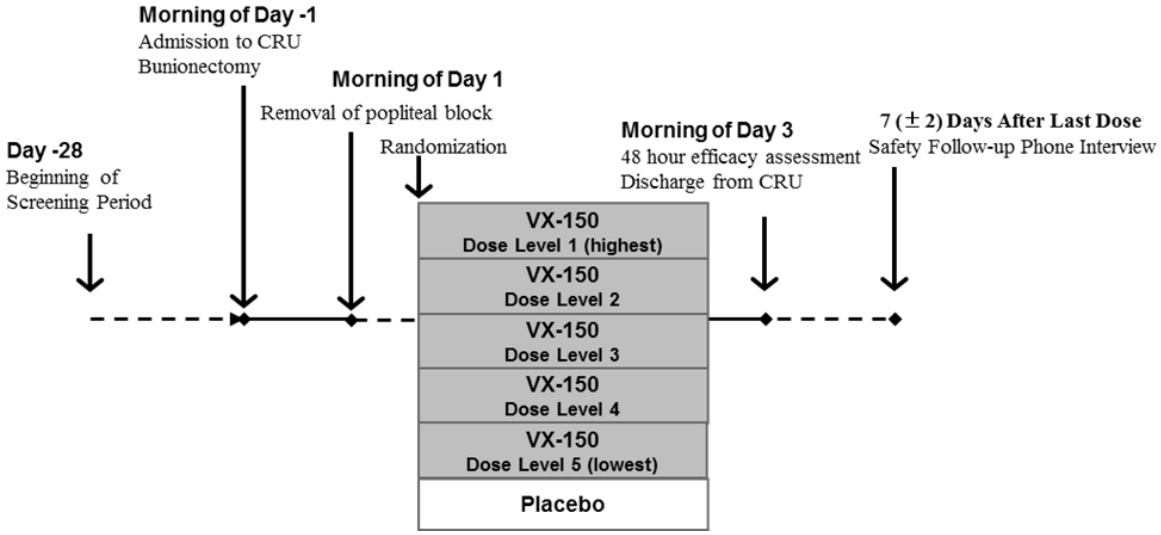
Treatment	Dose Level	Dose	Number of Subjects
VX-150	1 (highest)	First dose 1500 mg, then 750 mg q12h	44
	2	1000 mg qd	44
	3	500 mg q12h	44
	4	First dose 500 mg, then 250 mg q12h	44
	5 (lowest)	250 mg qd	22
Placebo			44

q12h: every 12 hours; qd: daily
Note: q12h dosing will be through 36 hours after the first dose of study drug throughout the protocol.

Subjects will report their pain on the NPRS at scheduled time points (See Table 3-2 in CSP) through 48 hours after the first dose of study drug. In addition, pain intensity will be recorded

on the NPRS immediately before each administration of rescue medication. Subjects are encouraged to wait 90 minutes after the first dose of study drug to receive rescue medication, and subjects should generally not receive rescue medication unless their NPRS is ≥4. However, subjects may receive rescue medication at any time after the first dose of study drug per their request. The rescue medication will be ibuprofen (400 mg [oral] every 4 hours [q4h] as needed [prn]).

Figure 7-1 VX18-150-104 Study Design



CRU: clinical research unit; NPRS: Numeric Pain Rating Scale; VRS: Verbal Categorical Rating Scale
Notes: After removal of the popliteal sciatic block, a subject can be randomized once the subject requests the first dose of study drug for pain relief, and the subject's pain is ≥4 on the NPRS and is moderate or severe on the VRS. VX-150 dose levels (Dose Levels 1 [highest], 2, 3, 4, and 5 [lowest]) are shown in Table 7-1. To maintain the blind, all subjects will receive the same number of capsules.

7.2 Sample Size and Power

The sample size calculation is based on the primary analysis of the primary efficacy endpoint. The primary efficacy endpoint is the time-weighted sum of the pain intensity difference 0 to 24 hours after the first dose (SPID24). The primary analysis of this endpoint is to detect if there is a significant dose-response relationship across VX-150 dose groups and placebo using the MCP-Mod (multiple comparison procedures with modeling techniques). Under MCP-Mod, a pre-specified candidate set of 4 dose-response models (Linear, Emax, Logistic, and Sigmoid Emax) is proposed.

Assuming the maximum effect size compared to placebo is 0.7, 40 evaluable subjects in the placebo, VX-150 Dose Level 1 (highest), 2, 3, and 4 groups, and 20 evaluable subjects in VX-150 Dose Level 5 (lowest) group would provide approximately at least 88% power to detect a dose-response relationship from the candidate set with a 5% level of significance. In addition, 40 evaluable subjects per treatment group can provide at least 85% power to detect an effect size of 0.7 compared to placebo. In order to allow for withdrawal of up to 10% of randomized subjects, the study will enroll and randomize approximately 242 subjects in total.

7.3 Randomization

A total of approximately 242 subjects will be randomized 2:2:2:2:1:2 to 6 treatment arms. Randomization will be stratified by site and sex. To maintain the blind, all subjects will receive the same number of capsules in a double-dummy design.

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

Refer to Section 10.7 of the CSP for details.

8 ANALYSIS SETS

8.1 All Subjects Set

The **All Subjects Set** will be 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)** will be defined as all randomized subjects who have received at least 1 dose of study drug. The FAS will be used to summarize subject demographics, baseline characteristics, and for all efficacy analyses in which subjects will be analyzed according to their randomized treatment group.

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 will be used for all safety analyses in which subjects will be analyzed according to the treatment they received.

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.

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

Categorical variables will be summarized using counts and percentages.

Baseline value for NPRS will be defined as the most recent non-missing measurement collected on Day 1 before the first dose of study drug. For all other variables, unless

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

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 first dose of study drug through the Safety Follow-up (for enrolled subjects who do not have a Safety Follow-up Phone Interview: it will be defined as the time from first dose of study drug through 9 days after the last dose of study drug)

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 and minimum values during TE period, and maximum and minimum change from baseline values during TE period 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 be imputed for NPRS by applying linear interpolation to the valid observations immediately before and after the missing observation(s). If there are no valid observations after the missing observation(s) the last observation carried forward (LOCF) principle will be applied as a primary approach. Additional details on how to handle missing data is described in subsequent sections when applicable.

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

Multiplicity: No multiplicity adjustment will be performed for hypothesis testing except for MCP-Mod procedure in Section 9.3.1.2 and 9.3.1.3. [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:

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

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

9.2.2 Demographics and Baseline Characteristics

Demographics 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)
- [redacted]

Disease characteristics will include the following:

- Pain intensity at baseline as recorded on the NPRS
- VRS at baseline

In addition, data listings will also be provided for:

- Inclusion/Exclusion criteria violation for subjects with any such violations
- Supplemental analgesic medications administered after surgery and before removal of the popliteal sciatic block

9.2.3 Medical History

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). For the FAS, medical history will be summarized descriptively by system organ class (SOC) and preferred term (PT). The corresponding data listing will also be provided.

9.2.4 Prior and Concomitant Medications

Medications taken 14 days before the Screening Visit and up to the Safety Follow-up will be 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 completely missing or partially missing start/stop dates and it cannot be determined whether it was taken before the first dose or concomitantly, it will be classified as prior and concomitant.

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

9.2.5 Study Drug Exposure and Study Drug Compliance

Study drug will be administered to the subjects by site personnel at time points specified in Table 3-2 and as described in Section 9.6 of CSP during a period of 36 hours. Therefore, it is not needed to perform a calculation of exposure to study drug or a calculation of compliance. All data collected during dispensation of study drug, i.e. time of administration and number of capsules taken, will be presented in an individual data listing only.

9.2.6 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 time-weighted sum of the pain intensity difference 0 to 24 hours (SPID24) after the first dose of VX-150 or placebo.

In general SPID is calculated as: $\sum \Delta time_i \times PID_i$

Where:

- $\Delta time_i$ = time (in hours) elapsed since previous measurements
- PID_i = pain intensity at baseline when the subject requests the first dose of study medication - pain intensity at hour i

Hence:

- $SPID24 = 0.5 \times PID_{0.5} + 0.5 \times PID_1 + 0.5 \times PID_{1.5} + 0.5 \times PID_2 + PID_3 + PID_4 + PID_5 + PID_6 + 2 \times PID_8 + 4 \times PID_{12} + 4 \times PID_{16} + 4 \times PID_{20} + 4 \times PID_{24}$

As stated in Section 9.1, intermittent missing data will be imputed for NPRS by applying linear interpolation to the valid observations immediately before and after the missing observation(s) during 0 to 48 hours. Such intermittent missing data are assumed to be missing completely at random.

Pain intensity scores that were collected within 4 hours after a dose of rescue medication (rescue period) will not be used in the analysis. Instead, these observations will be imputed with the pain assessment completed immediately before the administration of rescue medication. If that pain assessment is missing, the last non-missing regular pain intensity score will be applied (the LOCF principle). This approach assumes that the effect of the study drug on pain intensity score remains the same as the pre-rescue measurement during the first 4 hours after administration of rescue medication.

If there are multiple administrations of rescue medication within the same 4 hour period, a local highest pain intensity score will be used for the imputation during the second 4 hours rescue period. The local highest pain intensity score is the highest values among the first pre-rescue, the second pre-rescue and the actual observed (if any) in the overlapping period.

If a subject discontinues the study drug treatment prior to 24 hours, the LOCF principle will be used to impute all pain intensity scores up to 24 hours, irrespective of reason for study drug treatment discontinuation so that SPID24 can be calculated accordingly. Even if a subject completes the study, but has missing data from a certain time point to hour 24, the LOCF principle will be used to impute all pain intensity scores up to 24 hours. The last observed pain intensity score should be from a regularly scheduled measurement including a previous pre-rescue assessment, but cannot be any actual measurements taken during a previous rescue period. The LOCF principle assumes that the last observed pain intensity score represents the effects of study drug in the remaining of study period towards the

planned endpoint, regardless of reason for discontinuation and if the subject completes the study or not.

The imputation order will be: (1) intermittent missing data (2) 4 hours after administration of rescue medication and (3) missing data from a certain time point towards the planned endpoint including after early discontinuation from study drug treatment.

9.3.1.2 Primary Analysis

The primary efficacy analysis will be using the MCP-Mod approach to detect the dose-response relationship from a candidate set of 4 dose-response models (Linear, Emax, Logistic, and Sigmoid Emax). Dose level 2 and Dose level 3 of VX-150 group will be combined into one treatment group in the MCP-Mod procedure. Total dose on Day 1 for each treatment group will be used in the MCP-Mod procedure as shown in Table 9-1.

Table 9-1 VX-150 Doses by Treatment in Primary Analysis

Treatment	Dose Level	Dose	Total Dose on Day 1	Analysis Treatment Group
VX-150	1 (highest)	First dose 1500 mg, then 750 mg q12h	2250 mg	VX-150 Dose Level 1
	2	1000 mg qd	1000 mg	VX-150 Dose Level 2/3
	3	500 mg q12h		
	4	First dose 500 mg, then 250 mg q12h	750 mg	VX-150 Dose Level 4
	5 (lowest)	250 mg qd	250 mg	VX-150 Dose Level 5
Placebo			0 mg	Placebo

MCP-Mod approach will be based on an analysis of covariance (ANCOVA) model. The model will include SPID24 after the first dose as the dependent variable, treatment as a fixed effect, with site, sex, and baseline pain intensity score as covariates. The Least Squares (LS) means (SE) and 95% confidence interval (CI) will be provided for each treatment group. From the MCP-Mod procedure, the 2-sided *P* value will be provided for each dose-response model in the candidate set. If at least one dose-response model in the candidate set is statistically significant, a dose-response model will be selected based on the maximum test statistic criterion. The selected dose-response model will be estimated and presented in a figure.

Pain intensity scores used for the primary analysis will be summarized descriptively including SE by treatment at each scheduled time point and the mean values over time by treatment will be presented in a figure. SPID24 used for the primary analysis will also be summarized descriptively including SE by treatment.

[redacted]

[redacted]

9.3.2 Analysis of Secondary Efficacy Variables

9.3.2.1 Definition of Secondary Efficacy Variables

Time-weighted sum of the pain intensity difference between VX-150 versus placebo as recorded on a NPRS 0 to 48 hours (SPID48) after the first dose: SPID48 will be calculated using the following formula:

- $SPID48 = 0.5 \times PID_{0.5} + 0.5 \times PID_{1} + 0.5 \times PID_{1.5} + 0.5 \times PID_{2} + PID_{3} + PID_{4} + PID_{5} + PID_{6} + 2 \times PID_{8} + 4 \times PID_{12} + 4 \times PID_{16} + 4 \times PID_{20} + 4 \times PID_{24} + 4 \times PID_{28} + 4 \times PID_{32} + 4 \times PID_{36} + 4 \times PID_{40} + 4 \times PID_{44} + 4 \times PID_{48}$

Proportions of subjects with at least 30%, 50%, or 70% reduction in NPRS at 24 hours after the first dose of VX-150 versus placebo: A subject with at least 30%, 50%, or 70% reduction in NPRS at 24 hours after the first dose of study drug will be defined as a "responder". The percentage reduction in the NPRS will be calculated as following:

- 100 × (NPRS at baseline −NPRS at 24 hours) / NPRS at baseline

If a subject discontinues the study drug treatment for any reason prior to 24 hours, this subject will not be a "responder" for any of the three criteria. If a subject has missing NPRS at 24 hours without discontinuing the study drug treatment prior to 24 hours, the LOCF principle will be used to impute pain intensity score at 24 hours. The last observed pain intensity score should be from a regularly scheduled measurement including a previous pre-rescue assessment, but cannot be any actual measurements taken during a previous rescue period.

Time to onset of "confirmed perceptible pain relief" and "meaningful pain relief" after the first dose of VX-150 versus placebo: Time to onset of "perceptible pain relief" is the time elapsed from first dose of VX-150 or placebo until the subject stops the "perceptible pain relief" stopwatch. Time to onset of "meaningful pain relief" is the time elapsed from first dose of VX-150 or placebo until the subject stops the "meaningful pain relief" stopwatch. Time to onset of "confirmed perceptible pain relief" will be defined as the time to onset of perceptible pain relief for those subjects who had meaningful pain relief.

If the subject has not stopped the stopwatch by 6 hours after the first dose, the stopwatch will be stopped and time to onset will be considered censored at 6 hours. If the subject receives rescue medication during the first 6 hours, the stopwatch will be stopped immediately before administration of rescue medication and time to onset will be considered censored at the time of rescue medication plus 4 hours or at 6 hours, whichever happened earlier. If perceptible pain relief is obtained without associated meaningful pain relief, time to onset of "confirmed perceptible pain relief" will also be considered censored at 6 hours.

9.3.2.2 Secondary Analyses

Time-weighted sum of the pain intensity difference between VX-150 versus placebo as recorded on a NPRS 0 to 48 hours (SPID48) after the first dose: Same imputation strategies as described for SPID24 in Section 9.3.1.1 will be applied to SPID48. [redacted]

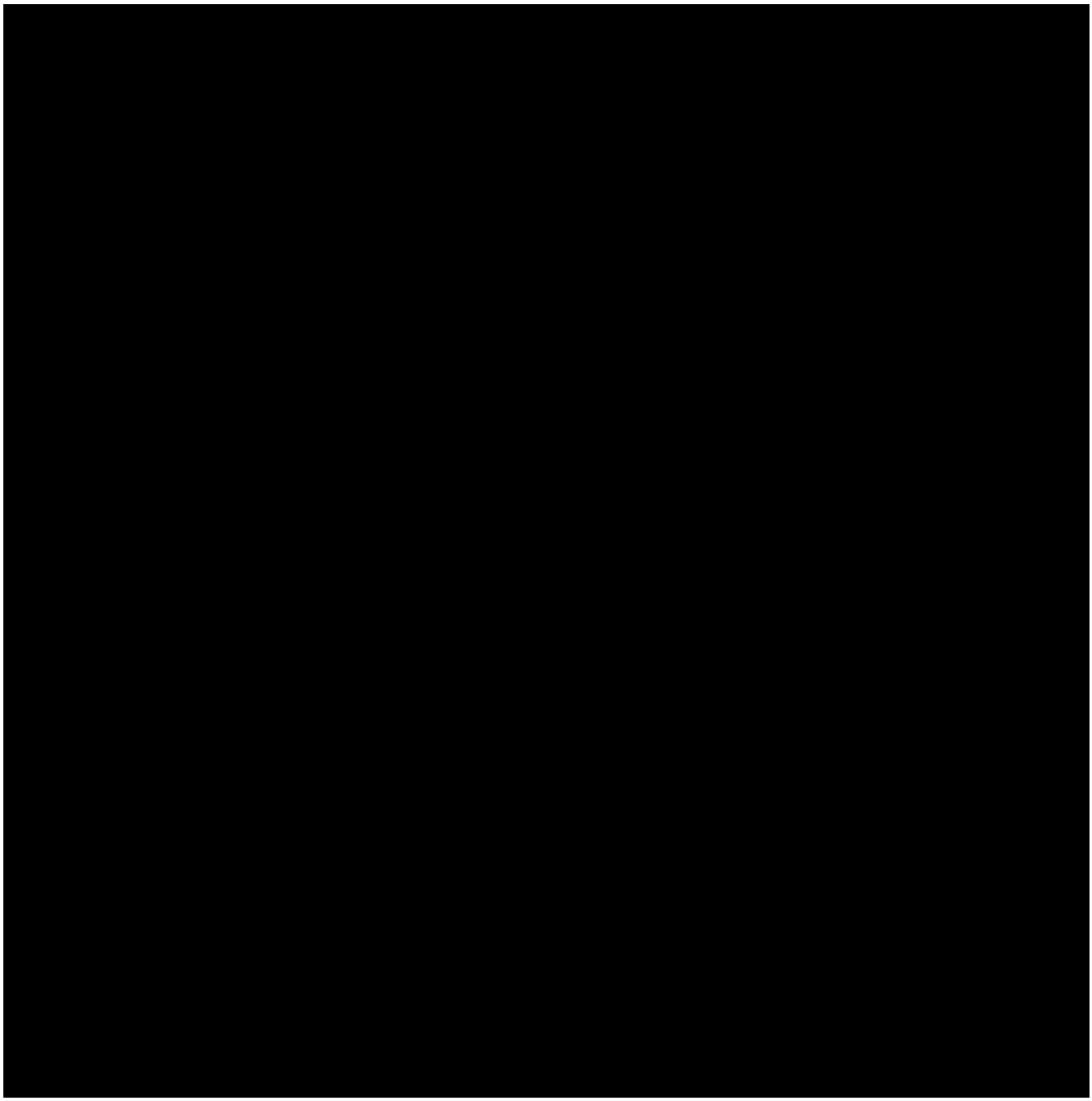
Proportions of subjects with at least 30%, 50%, or 70% reduction in NPRS at 24 hours after the first dose of VX-150 versus placebo: Analysis of responder rates between each individual dose level of VX-150 and placebo will be conducted using Cochran-Mantel-Haenszel test, stratified by site and sex.

Time to onset of "confirmed perceptible pain relief" and "meaningful pain relief" after the first dose of VX-150 versus placebo: Time to onset of "confirmed perceptible pain relief" will be analyzed using Cox regression model. The model will include treatment, site and sex as covariates. Pairwise comparison between each individual dose level of VX-150 and placebo will be conducted under the model.

Note: If placebo group has fewer than 5 subjects experience “confirmed perceptible pain relief”, the Cox regression will not be performed. If any dose level of VX-150 group has fewer than 5 subjects experience “confirmed perceptible pain relief”, the particular dose level group will not be included in the Cox regression model.

Additionally, the Kaplan-Meier method will be used to produce graphical presentation of the survival curves by treatment group.

Time to onset of “meaningful pain relief” and time to onset of “perceptible pain relief” will be analyzed in the same way as described for time to onset of “confirmed perceptible pain relief”.



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 (hematology, serum chemistry, coagulation studies, and urinalysis)
- ECG outcomes
- Vital signs

Safety analyses will be based on the Safety Set.

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, if the subject receives more than one dose level of VX-150, the actual treatment is defined as the highest dose level among all received VX-150 treatment, regardless of the randomized treatment assignment. For any dosed subjects, 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 of study drug through the end of the TE period.

Details for imputing missing or partial start date and time 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 and study drug treatment 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. Hematology and clinical chemistry results at baseline will be summarized by treatment group. Other assessments will be collected as needed, i.e. at unscheduled visits. The threshold value criteria for hematology and clinical chemistry laboratory tests are provided in Appendix D. A listing containing individual subject hematology and clinical chemistry measurements meeting the threshold value criteria at any visit will be provided. For each subject in the listing, measurements at all visits will be included. Results of coagulation, urinalysis and 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 time point 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 ≤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 time point will be provided. For each subject in the listing, ECG measurements at all time points will be included.

Clinically significant ECG abnormalities occurring during the study through the Safety Follow-up 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 Physical Examination

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

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/Time Point[1]	Target Study Day /Time Point per the protocol	Analysis Visit Window (in study days/ time points)
Safety Assessment			
Hematology Serum Chemistry Coagulation	Baseline	-1	[Screening visit, Pre-dose Day 1]
Standard 12-Lead ECG	Baseline	1	[Screening visit, Pre-dose Day 1]
	Day 1, 4 hours	4 hours after the first dose of study drug	3 – 5 hours after the first dose of study drug on Day 1
Vital Sign	Baseline	1	[Screening visit, Day 1]
	Day 2	2	2
	Day 3	3	3
Efficacy Assessment			
NPRS	Baseline	1	[After removal of the popliteal sciatic block, Pre-dose Day 1]
	At 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours	1 - 3	± 5 minutes for 0.5 to 12 hours ± 10 minutes for 16 to 48 hours
VRS	Baseline	1	[After removal of the popliteal sciatic block, Pre-dose Day 1]

[redacted]

[1] Visit/Time point name for analysis purpose is used to report data in tables and figures.

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/time point will be used; or
      ii. If there are multiple measurements within the same distance from the target day/time point, 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/time point will be used; or

ii. If there are multiple measurements within the same distance from the target day/time point, 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 hour and/or minute of first dose time are missing, baseline will be defined as the most recent non-missing measurement collected before the date of first dose of study drug.
4. For vital sign, if scheduled and unscheduled measurements at the same date, the scheduled measurement will be used.
5. Age (in years) at first dose date (for demographics, listing):

   Obtain the age at screening visit (in days) in "yy, mm" format (e.g., 24 years, 6 months) from the Vital Signs (VS) page at the Screening Visit, and add 0.5 month to convert to days.

   Obtain the screening visit date.

   Then age (in years) at first dose = [(first dose date– screening visit date) in days + age at screening visit (in days)]/365.25.

Appendix B: Imputation Rules for Missing Prior/Concomitant Medication Date

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

1. Missing or partial medication start date and time:
    a. If Hour and/or Minute are missing, do not impute.
    b. If DAY is missing, use the first day of the month.
    c. If DAY and Month are both missing, use the first day of the year.
    d. 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.

With missing or partial medication start time, only use the imputed start date to categorize the prior and/or concomitant medication as described in Table 12-2. If hour and/or minute of first dose time are missing, only use the first dose date to categorize the prior and/or concomitant medication.

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 Date and Time

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

If Hour and/or Minute of AE start time are missing, do not impute:

- If the AE start date is before the first dose date, the AE will be classified as pretreatment AE.
- If the AE start date is on or after the first dose date, the AE will be classified as TEAE.

If Day of AE start date is missing:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then
    - if the AE start year and month are equal to the month and year of first dose date, then impute the AE start day as the day of first dose date;
    - else impute the AE start day as 1.
- Else 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 the full (or partial) AE end date is NOT before the first dose date or AE end date is missing,
    - if AE start year is equal to the year of the first dose date, then impute the AE start month and day as the month and day of first dose date.
    - else impute the AE start Month as January and the Day as 1.
- Else 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.

If hour and/or minute of first dose time are missing:

- If the AE start date is before the first dose date, the AE will be classified as pretreatment AE.
- If the AE start date is on or after the first dose date, the AE will be classified as TEAE.

Appendix D: Threshold Value Criteria

Table 12-3 Threshold Value Criteria for Laboratory Tests

Parameter	Thresholds	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.
CPK	>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	Thresholds	Comments
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.
Albumin	≤25 g/L	
Amylase	>2.0 to 5.0 x ULN >5.0 x ULN	Criteria based upon CTCAE
Lipase	>2.0 to 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	>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	Thresholds	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	Absolute values (ms) Borderline prolonged: 431-450 ms (Male); 451-470 ms (Female) Prolonged : >450 ms (Male); >470 ms (Female) Increase from baseline Borderline prolonged: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula.

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

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