*VERTEX PHARMACEUTICALS INCORPORATED*

# Statistical Analysis Plan (Final Analysis): Methods

## Protocol Number VX16-150-103 (Final Analysis)

### A Phase 2 Randomized, Double-blind, Placebo controlled, 3-arm, Parallel-design Study of the Efficacy and Safety of VX-150 for Acute Pain Following Bunionectomy

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**Version:** 1.0
**Version Date of SAP:** 15 Dec 2017

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# 1 TABLE OF CONTENTS

# 3 INTRODUCTION

This statistical analysis plan (SAP) Methods document for the final analysis is based on the approved clinical study protocol (CSP), dated 30 AUG 2017, Version 3.0, final electronic case report form (eCRF) completion guidelines, Version 1.0, dated 9 JUN 2017, and approved eCRF, Version 2.0, dated 12 JUN 2017.

Study VX16-150-103 is a proof-of-concept study that will evaluate the efficacy, tolerability, PK and safety of VX-150 in the treatment of acute pain. Bunionectomy was selected for this study because it is a well-established, surgical, acute pain model that has been used for both proof-of-concept and registration studies.

This SAP (Methods) documents the planned final statistical analysis of efficacy and safety endpoints defined in the study protocol of VX16-150-103 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 data lock for the final analysis. 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).

# 4 STUDY OBJECTIVES

## 4.1 Primary Objective

To evaluate the efficacy of VX-150 in treating acute pain following bunionectomy.

## 4.2 Secondary Objectives

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

[redacted]

# 5 STUDY ENDPOINTS

## 5.1 Efficacy Endpoints

### 5.1.1 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 after the first dose

### 5.1.2 Secondary Efficacy Endpoints

- Time-weighted sum of the pain intensity difference between VX-150 versus placebo as recorded on a NPRS 2 to 24 hours after the first dose
- Time-weighted sum of the pain intensity difference between VX-150 versus placebo as recorded on a NPRS 0 to 48 hours after the first dose
- Time to onset of "perceptible pain relief" and "meaningful pain relief" after the first dose of VX-150 versus placebo
- Time to first rescue medication after the first dose of VX-150 versus placebo
- Percentage of subjects using rescue medication, and total rescue medication use, 0 to 24 hours after the first dose VX-150 versus placebo
- Percentage of subjects using rescue medication, and total rescue medication use, 24 to 48 hours after the first dose VX-150 versus placebo

### 5.2 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

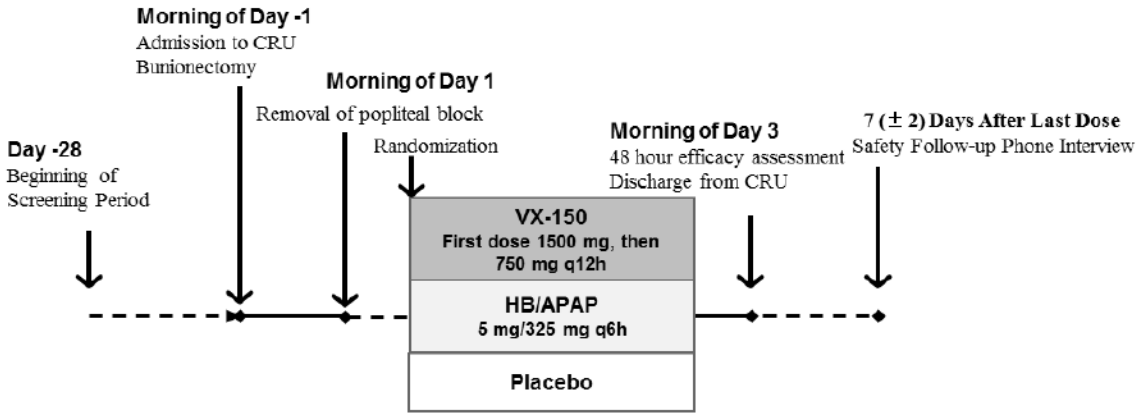
## 6 STUDY DESIGN

### 6.1 Overall Design

This is a Phase 2 randomized, double-blind, placebo-controlled, 3-arm, parallel-design study. Subjects will receive a primary unilateral first metatarsal bunionectomy repair on Day -1 (Figure 6-1). A continuous popliteal sciatic block infusion (0.2% ropivacaine) will be started after surgery, and remain in place until approximately 3AM 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 Verbal Categorical Rating Scale (VRS). 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.

Subjects will report their pain on the NPRS at scheduled time points (Table 11-2) 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] q4h as needed [prn]).

**Figure 6-1 VX16-150-103 Study Design**




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. To maintain the blind, all subjects will receive the same number of capsules.

## 6.2 Sample Size and Power

The sample size calculation is based on the primary efficacy analysis, i.e., the comparison between VX-150 and placebo.

The primary efficacy endpoint is the time-weighted sum of the pain intensity difference 0 to 24 hours after the first dose. The null hypothesis to be tested is that the mean time-weighted sum of the pain intensity difference 0 to 24 hours after the first dose is the same for VX-150 and placebo treatment groups.

Assuming a standard deviation of 20, 64 subjects completing the study per treatment group would provide about 80% power to detect a treatment difference of 10 between VX-150 and placebo (effect size of 0.5) in mean time-weighted sum of the pain intensity difference over the first 24 hours after the first dose with a 5% level of significance. In order to allow for withdrawal of up to 20% of randomized subjects over the first 24 hours after the first dose, the study will enroll and randomize approximately 80 subjects per treatment group.

## 6.3 Randomization

A total of approximately 240 subjects will be randomized 1:1:1 to VX-150, placebo, or HB/APAP; randomization will be stratified by site and sex. The first dose of VX-150 will be 1500 mg, followed by 750 mg every 12 hours (q12h). The dose of HB/APAP will be 5 mg/325 mg every 6 hours (q6h). To maintain the blind, all subjects will receive the same number of capsules in a double-dummy design.

An interactive web or voice response system (IXRS) will be used to assign subjects to treatment. The randomization code will be produced by 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.

## 6.4 Blinding and Unblinding

This will be a double-blind study.

### 6.4.1 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 Clinical research Unit (CRU) 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 execution team

- Vertex IXRS Management for IXRS oversight and system administration
- Vertex Clinical Supply Chain
- The bioanalytical laboratory/vendor personnel providing sample testing for the study

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

Vertex bioanalytical monitors will be unblinded to allow real time review of bioanalytical data. The Vertex bioanalytical monitors will not be members of the study team, and will not interact with the 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 dataset is being provided for preliminary analysis. This individual will not be a member of the study team, and will not interact with the CRU or study personnel. Masked IDs will be used for these analyses.

### 6.4.2 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.

## 7 ANALYSIS SETS

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

### 7.1 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.

### 7.2 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.

### 7.3 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.

### 7.4 Screen Failure Analysis Set

The Screen Failure Analysis Set is defined as all subjects who completed the surgery but were not randomized and did not receive any study drug. This analysis set will be used to present a limited amount of data in tables and/or listings.

## 8 STATISTICAL ANALYSIS

### 8.1 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, 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.

**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 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 it will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the initial administration 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.

**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 B.

**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 specified otherwise.

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

## 8.2 Background Characteristics

### 8.2.1 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 Phone Interview or 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.

### 8.2.2 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 (female and male)

- 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 ($kg/m^2$)

Disease characteristics will include the following:

- Pain intensity on Day -1 as recorded on the NPRS
- Pain intensity at baseline as recorded on the NPRS
- Pain intensity at baseline as recorded on the VRS

Medical history will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT).

### 8.2.3 Prior and Concomitant Medications

Medications taken 14 days before the Screening Visit and up to the Safety Follow-up will be summarized by Preferred Name using the World Health Organization-Drug Dictionary Enhanced (WHO-DDE, March 1, 2017) 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 C.

### 8.2.4 Study Drug Exposure and Study Drug Compliance

All study drugs will be given to the subjects by site personnel at eight different times during a period of 42 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 intake and number of capsules taken, will be presented in data listings only.

### 8.2.5 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 G.

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

### 8.2.6 Data for Screen Failures

The following data will be summarized overall based on the Screen Failure Set

- Age (in years)
- Sex (female and male)
- Inclusion criteria not met
- Exclusion criteria met
- Site
- Pain intensity on Day -1 as recorded on the NPRS
- Pain intensity on Day 1 as recorded on the NPRS
- Pain intensity on Day 1 as recorded on the VRS

If there are multiple measurements collected for NPRS and VRS on Day 1, select the most recent non-missing measurement. The same data will also be presented in individual subject data listings.

## 8.3 Efficacy Analysis

The primary efficacy analysis in this study aims an effectiveness estimand that would assess effectiveness at planned endpoint using the time-weighted sum of the pain intensity difference (SPID), focusing on the causal effects attributable to the initially randomized treatments without the effects of possible rescue medication usage.

Such an estimand hypothetically aims the treatment effects of the initial randomization only rather than any other treatment regimen including (inevitable) rescue medication usage after randomization. With such an estimand, all subjects in FAS with their primary efficacy endpoint data up to the planned time point would have been used even with possible rescue periods and discontinuation of initial randomized treatments. Due to the expectation of free confounding effects from rescues, pain intensity scores that were collected during certain

rescue period will not be used in the calculation of SPID and need to be imputed under some assumptions. Any missing data will be imputed up to the planned time point. For both primary efficacy analysis [redacted] of primary efficacy variable, the imputation methods and the corresponding assumptions will be articulated in the following sections when applicable.

[redacted]

### 8.3.1 Analysis of Primary Efficacy Variable

#### 8.3.1.1 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 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 8.1, intermittent missing data will be imputed for NPRS by applying linear interpolation to the valid observations immediately before and after the missing observation(s). Such intermittent missing data are assumed to be completely random.

Pain intensity scores that were collected within 4 hours after a dose of rescue medication (rescue period) will not be used in the primary 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 intake 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 in the overlapping period.

If a subject discontinues the study drug, the LOCF principle will be used to impute all pain intensity scores up to 24 hours, irrespective of reason for study drug discontinuation so that

SPID24 can be calculated accordingly. Even if a subject completes the study, but has missing data from a certain timepoint to hour 24, the LOCF principle will be used to impute all pain intensity scores up to 24 hours. The last observed PI 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 intake of rescue medication and (3) missing data from a certain timepoint towards the planned endpoint including after early discontinuation from study drug. All imputation strategies would support the primary efficacy analysis estimand under stated assumptions.

#### 8.3.1.2 Primary Analysis

The primary efficacy analysis will be based on an analysis of covariance (ANCOVA) model of the primary efficacy endpoint. The model will include the SPID24 as the dependent variable, baseline pain as a continuous covariate, and treatment as a fixed effect, with adjustment for stratification factors, i.e., site and sex.

The primary result obtained from the model will be the Least Squares (LS) mean as treatment effect over 0 to 24 hours after the first dose. The treatment effect difference in LS mean, a 95% confidence interval for the difference, and a 2-sided *P* value will be provided.

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

[redacted]

[redacted]

### 8.3.2 Analysis of Secondary Efficacy Variables

#### 8.3.2.1 Definition of Secondary Efficacy Variables

- Time-weighted sum of the pain intensity difference over 2 to 24 hours (SPID22) after the first dose of VX-150 or placebo will be calculated using the following formula:
    - $SPID22 = PID_3 + PID_4 + PID_5 + PID_6 + 2 \times PID_8 + 4 \times PID_{12} + 4 \times PID_{16} + 4 \times PID_{20} + 4 \times PID_{24}$
- Time-weighted sum of the pain intensity difference over 0 to 48 hours (SPID48) after the first dose of VX-150 or placebo will be calculated using the following formula:
    - $SPID48 = 0.5 \times PID_{0.5} + 0.5 \times PID_1 + 0.5 \times PID_{1.5} + 0.5 \times PID_2 + PID_3 + PID_4 + PID_5 + PID_6 + 2 \times PID_8 + 4 \times PID_{12} + 4 \times PID_{16} + 4 \times PID_{20} + 4 \times PID_{24} + 4 \times PID_{28} + 4 \times PID_{32} + 4 \times PID_{36} + 4 \times PID_{40} + 4 \times PID_{44} + 4 \times PID_{48}$
- 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. If the subject has not stopped the stopwatch by 6 hours after the first dose, the stopwatch will be stopped. If the subject receives rescue medication during the first 6 hours, the stopwatch will be stopped immediately before administration of rescue medication. For those subjects, time to onset will be considered censored at the time the stopwatch is stopped plus 4 hours or at 6 hours, whichever happened earlier. If a subject discontinues from the study after the first six hours after the first dose of study medication, time to onset will be considered censored at 6 hours. If it can't determined that whether a subject discontinues from the study within 6 hours after the first dose of study medication, time to onset will be considered censored at 6 hours.
- 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. If the subject has not stopped the stopwatch by 6 hours after the first dose, the stopwatch will be stopped. If the subject receives rescue medication during the first 6 hours, the stopwatch will be stopped immediately before administration of rescue medication. For those

subjects, time to onset will be considered censored at the time the stopwatch is stopped plus 4 hours or at 6 hours, whichever happened earlier. If a subject discontinues from the study after the first six hours after the first dose of study medication, time to onset will be considered censored at 6 hours. If it can't determined that whether a subject discontinues from the study within 6 hours after the first dose of study medication, time to onset will be considered censored at 6 hours.

- Time to first rescue medication is the time elapsed from first dose of VX-150 or placebo until the subject receives the first dose of rescue medication. If the subject does not receive any rescue medication during the 48 hour treatment period, time to first dose will be considered censored at 48 hours.
- The proportion of subjects with any use of rescue medication (Yes/No) within 24 hours after first dose of VX-150 or placebo will be evaluated in a categorical analysis.
- Total use of rescue medication during the period 0 to 24 hours will be calculated as the sum of number of capsules*strength at each dosing occasion.
- The proportion of subjects with any use of rescue medication (Yes/No) 24 to 48 hours after the first dose of VX-150 or placebo will be evaluated in a categorical analysis.
- Total use of rescue medication during the period >24 to 48 hours will be calculated as the sum of number of capsules*strength at each dosing occasion.

#### 8.3.2.2 Secondary Analyses

- SPID22 and SPID48 will be analyzed in the same way as described for SPID24 after the same imputation strategies are applied as in Section 8.3.1.
- Time to onset of "perceptible pain relief" will be analyzed using Cox regression model. The model will include treatment, site and sex as covariates. Additionally, the Kaplan-Meier method will be used to estimate time to onset rates by treatment group and the associated plot will also be provided.
  Note: If in either treatment group fewer than 5 subjects experience "perceptible pain relief", the Cox regression will not be performed and analysis of time-to-first event will be restricted to the Kaplan-Meier estimates
- Time to onset of "meaningful pain relief" will be analyzed in the same way as described for time to onset of "perceptible pain relief".
- Time to first intake of rescue medication will be analyzed in the same way as described for time to onset of "perceptible pain relief".
- The proportion of subjects with any use of rescue medication during the period 0 – 2 hours, 0 – 24 hours as well as >24 – 48 hours after first dose of VX-150 or placebo will be analyzed using the Cochran-Mantel-Haenszel test, stratified by site and sex.
- Total rescue medication use 0 – 2 hours, 0 – 24 hours as well as >24 – 48 hours after the first dose of VX-150 or placebo will be analyzed using the Wilcoxon rank-sum test, stratified by site and sex.

[redacted]

## 8.4 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 (including coagulation studies)
- 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, 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 HB/APAP if the subject did not receive any VX-150 but receive any HB/APAP; the actual treatment is defined as placebo only if the subject receives placebo at all visits in the study.

### 8.4.1 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 start of study drug dosing through the Safety Follow-up.

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 worst relationship level will be presented in the relationship summary. Related adverse events include related, possibly related, and missing categories. So an AE with relationship missing is counted as related AE.

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

### 8.4.2 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 laboratory tests are provided in Appendix E. 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.

### 8.4.3 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, QTc for HR interval (QTcF [$QTcF = QT/RR^{0.33}$]), QRS duration, 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 ≤30 msec, >30 and ≤60 msec, and >60 msec, will be provided.

The threshold value criteria for ECG data are provided in Appendix E. 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 time points will be included.

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

### 8.4.4 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), HR (beats per minute), and respiratory rate (breaths per minute).

The threshold value criteria for vital signs data are provided in Appendix E. 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 time points will be included. Clinically significant abnormal findings in vital signs will be reported as AEs.

### 8.4.5 Physical Examination

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

### 8.4.6 Other Safety Analysis

Not applicable.

## 9 SUMMARY OF INTERIM AND IDMC ANALYSES

Not applicable.

# 10 REFERENCES

Guidance for Industry Analgesic Indications: Developing Drug and Biological Products, FDA DRAFT GUIDANCE, 2014.

Preventing and Treating Missing Data in Longitudinal Clinical Trials: A Practical Guide. Craig H. Mallinckrodt, Cambridge University Press, 2013.

The Prevention and Treatment of Missing Data in Clinical Trials. Panel on handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC: The national Academies. National Research Council. 2010.

# 11 LIST OF APPENDICES

## Appendix A: Schedule of Assessments

Schedules of Assessments are shown in Table 11-1 and Table 11-2.

**Table 11-1 Study VX15-150-103: Screening Period**

| Assessment | Screening Period Day -28 to Day -2 |
|---|---|
| Outpatient visit | X |
| Informed consent form (ICF) | X |
| Inclusion/exclusion criteria | X |
| Demographics | X |
| Medical history | X |
| History of drug and alcohol use | X |
| Weight, height, and body mass index (BMI)[a] | X |
| Vital signs[b] | X |
| Standard 12-lead electrocardiogram (ECG)[c] | X |
| Physical examination | X |
| Serum follicle-stimulating hormone (FSH)[d] | X |
| Serum β-hCG (all female subjects)[e] | X |
| Serology (HBsAg, HCV, and HIV 1/HIV 2)[f] | X |
| Serum chemistry[g] | X |
| Hematology[g] | X |
| Coagulation[g] | X |
| Urinalysis | X |
| Drug test (urine) | X |
| Medications review[h] | Continuous from signing of ICF through Safety Follow-up |
| Treatments and procedures | Continuous from signing of ICF through Safety Follow-up |
| Adverse events | Continuous from signing of ICF through Safety Follow-up |

[a] Weight and height will be measured with shoes off.
[b] Vital signs (pulse rate, respiration rate, blood pressure, and temperature) will be collected after the subject has been supine for at least 5 minutes and before any ECG or PK blood sampling.
[c] ECGs will be performed after subjects have been supine for at least 5 minutes. ECGs will be done after vital signs and before any procedures that may affect heart rate (e.g., blood sampling).
[d] Serum FSH is required for postmenopausal female subjects only.
[e] Serum β-hCG is required of all female subjects, and must be conducted within 7 days before Day 1.
[f] Serology includes testing for hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (HCV) and human immunodeficiency viruses 1 and 2 (HIV 1/HIV 2).
[g] Blood samples will be collected for clinical laboratory assessments following a fast of at least 4 hours.
[h] All medications taken within 28 days before screening through the end of the study will be recorded.

**Table 11-2 Study VX16-150-103: Day -1, Treatment Period, and Safety Follow-up**

| Event/Assessment | Day -1 | Day 1 | Day 2 | Day 3 | Safety Follow-up 7 (± 2) Days After Last Dose of Study Drug |
|---|---|---|---|---|---|
| Admission to CRU | X | | | | |
| Bunionectomy | X | | | | |
| Randomization | | X | | | |
| Study drug dosing[9] | | X | X | X | |
| Discharge from CRU[10] | | | | X | |
| Phone interview[11] | | | | | X |
| Vital signs[12] | X | X | X | X | |
| Standard 12-lead ECG | | X[13] | | | |
| Physical examination | X | | | | |
| β-hCG (urine) | X[14] | | | | |
| Serum chemistry | X[15] | | | | |
| Hematology | X[15] | | | | |
| Coagulation | X[15] | | | | |
| [redacted] | | | | | |
| PK blood sample | | X | X | X | |

[9] To maintain the blind, all subjects will receive the same number of capsules. The final dose of VX-150 or VX-150 placebo will be given 36 hours after the first dose, and the final dose of HB/APAP or HB/APAP placebo will be given 42 hours after the first dose.

[10] Subjects will be discharged on Day 3 after completion of the Day 3 assessments.

[11] The Safety Follow-up will consist of a phone interview for the purpose of collecting information on adverse events, medications, and treatments and procedures. A visit will only be required if a clinical finding during the Treatment Period requires follow-up.

[12] On dosing days, vital signs will be collected before the first dose of the day. Vital signs (pulse rate, respiration rate, blood pressure, and temperature) will be collected after the subject has been supine for at least 5 minutes and before any ECG or PK blood sampling.

[13] Standard 12-lead ECGs will be measured before the first dose, and at 4 (± 1) hours after the first dose on Day 1.

[14] A β-hCG test on Day -1 is only required for women of childbearing potential.

[15] If less than 1 week has passed since a subject completed the screening assessments, clinical chemistry, hematology, and coagulation do not need to be performed at Day -1.

[16] PK blood samples will be collected on Days 1 and 2 before the first dose of VX-150 or VX-150 placebo for the day and at 1, 2, 4, 6, 8, and 12 hours after the first dose of VX-150 or VX-150 placebo for the day. On Day 2, a PK blood sample will also be collected 12 hours after the second dose of VX-150 or VX-150 placebo for the day.

**Table 11-2 Study VX16-150-103: Day -1, Treatment Period, and Safety Follow-up**

| Event/Assessment | Day -1 | Day 1 | Day 2 | Day 3 | Safety Follow-up 7 (± 2) Days After Last Dose of Study Drug |
|---|---|---|---|---|---|
| Drug test (urine) | X | | | | |
| Alcohol test (breath) | X | | | | |
| NPRS[17] | X | X | X | X | |
| VRS[18] | | X | | | |
| Double-stopwatch assessment | | X | | | |
| Record rescue medication use | | X | X | X | |
| Medications review | Continuous from signing of ICF through Safety Follow-up | | | | |
| Treatments and procedures | Continuous from signing of ICF through Safety Follow-up | | | | |
| Adverse events | Continuous from signing of ICF through Safety Follow-up | | | | |

[17] On Day -1, subjects will report their pain on the NPRS scale before administration of preoperative/perioperative pain medications. Starting on Day 1, subjects will report their pain on the NPRS at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours (±5 minutes) after the first dose of study drug. In addition, pain intensity on the NPRS will be recorded when the subject requests the first dose of study drug for pain relief and immediately before each administration of rescue medication.

[18] On Day 1, subjects will report their pain on the VRS when they request the first dose of study drug for pain relief.

## Appendix B: Analysis Visit Windows for Safety and Efficacy Assessments

**Table 11-3 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<br>Serum Chemistry<br>Coagulation | Baseline | Day -1 | Before first dose of study drug |
| Standard 12-Lead ECG | Baseline | Day 1 | Before first dose of study drug |
| | Day 1 | 4 hrs. after first dose of study drug at Day 1 | 3 – 5 hours after first dose of study drug |
| Vital Signs | Baseline | Day 1 | |
| | Day 2 | Day 2 | |
| | Day 3 | Day 3 | |
| **Efficacy Assessment** | | | |
| NPRS | Day -1 | Day -1 | Before administration of preoperative/perioperative pain medications |
| | Baseline | Day 1, 0 hrs. | After removal of the popliteal sciatic block and before first dose of study drug |
| | Day 1 - Day 3 | 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hrs. after first dose of study drug at Day 1 | ± 5 minutes at each timepoint |
| VRS | Baseline | Day 1 | After removal of the popliteal sciatic block and before first dose of study drug |
| Rescue Medication | Day 1, Day 2 and Day 3 | Any time | After first dose of study drug |

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.

   c. When define efficacy and safety at baseline, refer to the generic baseline definition on Section 8.1. For vital sign, there is no time collected and Day 1 will be baseline.

## 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 and/or concomitant categorization of a medication is described below.

**Table 11-4 Prior and/orConcomitant 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 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, 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 E: Threshold Value Criteria

**Table 11-5 Threshold Value Criteria for Laboratory Tests**

| Parameter | | Comments |
|---|---|---|
| **Clinical Chemistry** | | |
| ALT | ≤3xULN*(Not a PCS criterion)<br>>3x to ≤ 5xULN<br>>5x to ≤ 8xULN<br>>3xULN<br>>5xULN<br>>8xULN | FDA DILI Guidance Jul 2009. |
| AST | ≤3xULN*(Not a PCS criterion)<br>>3x to ≤ 5xULN<br>>5x to ≤ 8xULN<br>>3xULN<br>>5xULN<br>>8xULN | FDA DILI Guidance Jul 2009. |
| ALT or AST | ALT>3xULN or AST>3xULN | Vertex LFT working group 2014.<br>To be counted within the same treatment period. |
| Alkaline Phosphatase | >1.5xULN | FDA DILI Guidance Jul 2009. |
| Total Bilirubin | >1.5x to ≤2xULN<br>>2xULN | FDA DILI Guidance Jul 2009. |
| ALT and Total Bilirubin | ALT>3xULN and TBILI>2xULN | FDA DILI Guidance Jul 2009.<br>To be counted within a same treatment period. |
| AST and Total Bilirubin | AST>3xULN and TBILI>2xULN | FDA DILI Guidance Jul 2009.<br>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.<br>To be counted within the same treatment period. |
| CPK | >3x to ≤ 10xULN<br>>10xULN | FDA criteria Feb 2005.<br>Am J Cardiol April 2006. |
| Creatinine | ≥150 µmol/L (Adults)<br>≥30% change from baseline<br>≥100% change from baseline | Benichou C., 1994. |
| Blood Urea Nitrogen | ≥17 mmol/L | |
| Chloride | <85 mmol/L<br>>115 mmol/L | |

**Table 11-5 Threshold Value Criteria for Laboratory Tests**

| Parameter | | Comments |
|---|---|---|
| Sodium | ≤129 mmol/L<br>≥150 mmol/L | |
| Potassium | <3 mmol/L<br>≥5.5 mmol/L | FDA Feb 2005. |
| Glucose<br>Hypoglycaemia<br>Hyperglycaemia | <br>≤3.9 mmol/L and <LLN<br>≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) | <br>ADA May 2005.<br>ADA Jan 2008. |
| Albumin | ≤25 g/L | |
| Amylase | >2.0 to 5.0 x ULN<br>>5.0 x ULN | Criteria based upon CTCAE |
| Lipase | >2.0 to 5.0 x ULN<br>>5.0 x ULN | Criteria based upon CTCAE |
| **Hematology** | | |
| WBC | <3.0 Giga/L (Non-Black); <2.0 Giga/L (Black)<br>≥16.0 Giga/L | Increase in WBC: not relevant.<br>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.<br>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)<br>≥185 g/L (Male); ≥165 g/L (Female)<br><br>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<br>≥700 Giga/L | International Consensus meeting on drug-induced blood cytopenias, 1991. |

**Table 11-6 Threshold Value Criteria for ECGs**

| Parameter | | Comments |
|---|---|---|
| HR | ≤50 bpm and decrease from baseline ≥10 bpm<br>≥120 bpm and increase from baseline ≥10 bpm | |
| PR | ≥220 ms and increase from baseline ≥20 ms | |
| QRS | ≥120 ms | |
| QTc<br>Borderline<br>Prolonged*<br>Additional | Absolute values (ms)<br>Borderline: 431-450 ms (Male); 451-470 ms (Female)<br>Prolonged: >450 ms (Male); >470 ms (Female)<br>≥500 ms<br><br>Increase from baseline<br>Borderline: Increase from baseline 30-60 ms<br>Prolonged: Increase from baseline >60 ms | To be applied to any kind of QT correction formula. |

Note: Based on CPMP 1997 guideline.

**Table 11-7 Threshold Value Criteria for Vital Signs**

| Parameter | PCS | Comments |
|---|---|---|
| HR | ≤50 bpm and decrease from baseline ≥20 bpm<br>≥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<br>≥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<br>≥110 mmHg and increase from baseline ≥10 mmHg | To be applied for all positions (including missing) except STANDING. |
| Orthostatic Hypotension<br>Orthostatic SBP<br>Orthostatic DBP | <br>≤-20 mmHg<br>≤-10 mmHg | |
| Weight | ≥5% increase from baseline<br>≥5% decrease from baseline | FDA criteria Feb 2007. |

## Appendix G: Important Protocol Deviation Categories

- Date Informed Consent Signed
- Inclusion/Exclusion Criteria Eligibility
- Randomization / Enrollment
- Missing/Out of Window Study Assessment
- Timing of Assessments
- Study Restrictions/ Withdrawal Criteria
- Dose Administration
- Sample Collection
- Safety Assessments