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VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX21-548-102 Version 3.0 (Final Analysis)

A Phase 2, Randomized, Double-blind, Placebo-controlled, Multi-dose Study Evaluating the Efficacy and Safety of VX-548 for Acute Pain After an Abdominoplasty

Author of SAP: [redacted]

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

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3 MODIFICATIONS

3.1 Modifications to the Approved Clinical Study Protocol

Not applicable

3.2 Modifications to the Approved Statistical Analysis Plan

Not applicable

4 INTRODUCTION

This statistical analysis plan (SAP) for the final analysis is based on the most recent approved clinical study protocol (CSP), the most recent approved electronic case report form (eCRF), and the most recent approved eCRF completion guidelines. This SAP documents the planned statistical analysis of efficacy and safety endpoints defined in the study protocol of VX21-548-102 and provides 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) will be finalized and approved before the clinical database lock for the final analysis. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP prior to the clinical database lock. Any revisions made to the SAP after the clinical database lock will be documented in the clinical study report for this study.

The analysis addressing the pharmacokinetic (PK) objective of the study will be described in the Clinical Pharmacology Analysis Plan (CPAP) which will be developed separately by the Clinical Pharmacology department at Vertex Pharmaceuticals Incorporated (Vertex).

5 STUDY OBJECTIVES

5.1 Primary Objective

- To evaluate the efficacy of VX-548 doses in treating acute pain after an abdominoplasty

5.2 Secondary Objective

- To evaluate the safety and tolerability of VX-548

5.3 Other Objectives

- To evaluate the pharmacokinetics (PK) of VX-548 and its metabolite, [redacted]

6 STUDY ENDPOINTS

6.1 Primary Endpoint

- Time-weighted sum of the pain intensity difference (SPID) as recorded on a Numeric Pain Rating Scale (NPRS) at rest 0 to 48 hours ($SPIDr_{0-48}$) after the first dose of study drug

6.2 Secondary Endpoints

- Time-weighted SPID as recorded on an NPRS at rest 0 to 24 hours ($SPIDr_{0-24}$) after the first dose of study drug
- Proportions of subjects with ≥30%, ≥50%, and ≥70% reduction in NPRS at rest at 48 hours after the first dose of study drug

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

6.3 Other Endpoints

- Time-weighted SPID as recorded on an NPRS during movement 8 to 24 hours ($SPIDm_{8-24}$) and 8 to 48 hours ($SPIDm_{8-48}$) after the first dose of study drug
- Time to onset of "confirmed perceptible pain relief" and "meaningful pain relief" after the first dose of study drug
- Proportions of subjects with ≥30%, ≥50%, and ≥70% reduction in NPRS at rest at 24 hours after the first dose of study drug
- Patient Global Assessment (PGA) of study drug at 48 hours after the first dose of study drug
- Percentage of subjects using rescue medication, and total rescue medication usage, 0 to 48 hours after the first dose of study drug
- PK parameter estimates of VX-548 and its metabolite, [redacted]

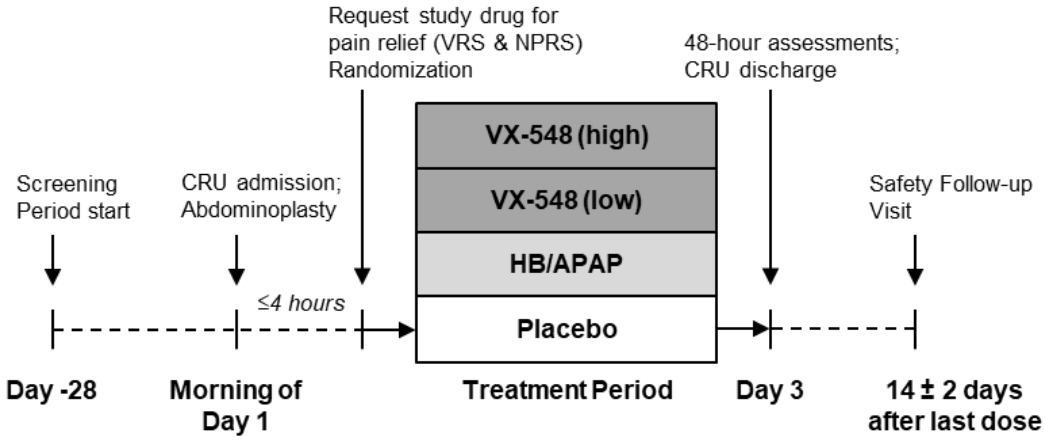
7 OVERALL DESIGN

This is a Phase 2, randomized, double-blind, placebo-controlled, 4-arm, parallel study design evaluating the efficacy and safety of VX-548 doses in treating acute pain after an abdominoplasty (Figure 7-1).

On Day 1, subjects will undergo a standard ("full") abdominoplasty procedure. After surgery completion, a subject will be randomized to 1 of 4 treatment groups if (1) the subject requests the first dose of study drug for pain relief, (2) the subject's pain is moderate or severe on the VRS at rest, and (3) the subject's pain is ≥4 on the NPRS at rest. If a subject does not meet the VRS and NPRS criteria within 4 hours of surgery completion, the subject will not be eligible for this study.

Approximately 256 subjects will be randomized 1:1:1:1 to 4 treatment groups: high-dose VX-548 (100 mg/50 mg every 12 hours [q12h]); low-dose VX-548 (60 mg/30 mg q12h); hydrocodone bitartrate/acetaminophen (HB/APAP; opioid reference); or placebo (Table 7-1). Randomization will be stratified by site and baseline NPRS at rest (<8 versus ≥8). To maintain the blind, all subjects will receive the same number of tablets and/or capsules every 6 hours (q6h) in a double-dummy design.

Figure 7-1 VX21-548-102 Study Design



CRU: clinical research unit; HB/APAP: hydrocodone bitartrate/acetaminophen; NPRS: Numeric Pain Rating Scale; q6h: every 6 hours; VRS: Verbal Categorical Rating Scale

Notes: After surgery completion, a subject will be randomized to 1 of 4 treatment groups if (1) the subject requests the first dose of study drug for pain relief, (2) the subject's pain is moderate or severe on the VRS at rest, and (3) the subject's pain is ≥4 on the NPRS at rest. If a subject does not meet the VRS and NPRS criteria within 4 hours of surgery completion, the subject will not be eligible for this study.

Table 7-1 VX21-548-102 Treatment Groups

Treatment	Active Dose	Number of Subjects
VX-548 (high dose)	100 mg first dose, then 50 mg q12h	64
VX-548 (low dose)	60 mg first dose, then 30 mg q12h	64
HB/APAP	5 mg/325 mg q6h	64
Placebo		64

HB/APAP: hydrocodone bitartrate/acetaminophen; q6h: every 6 hours; q12h: every 12 hours

Note: To maintain the blind, all subjects will receive the same number of tablets and/or capsules q6h in a double-dummy design. VX-548 active and/or VX-548 placebo will be administered to all subjects q12h: 0 hours (first dose) and at 12, 24 and 36 hours after the first dose of study drug. HB/APAP active or HB/APAP placebo will be administered to all subjects q6h: 0 hours (first dose) and at 6, 12, 18, 24, 30, 36 and 42 hours after the first dose of study drug.

Subjects will report their pain intensity on the NPRS at rest at each scheduled time point through 48 hours after the first dose of study drug. Starting 8 hours after the first dose of study drug, subjects will also report their pain intensity on the NPRS during movement. In addition, pain intensity will be recorded on the NPRS at rest immediately before each administration of rescue medication.

Ibuprofen (400 mg orally q6h as needed) is permitted as a rescue medication for pain relief upon the subject's request starting any time after the first dose of study drug through 48 hours after the first dose of study drug. Subjects are encouraged to wait 90 minutes after the first dose of study drug to request rescue medication, and subjects should generally not receive rescue medication unless their NPRS at rest score is ≥4.

7.1 Sample Size and Power

The sample size calculation is based on the comparison between VX-548 and placebo on the primary endpoint. Assuming a standardized effect size of 0.8 for VX-548 (high or low dose)

compared to placebo, 54 evaluable subjects per group would provide at least 90% power at a 2-sided significance level of 0.05. This sample size would allow a minimal detectable standardized effect size of 0.38 to achieve statistical significance between VX-548 (high or low dose) and placebo. With this sample size, a two-sided 95% CI for the estimated standard effect size will extend 0.38 from the observed standardized effect size, assuming the CI is based on the large sample z statistic. To allow for withdrawal of up to 15% of randomized subjects over 48 hours of treatment, the study will enroll and randomize approximately 256 subjects in total.

7.2 Randomization

Refer to Section 9.2 of the CSP for details.

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

8.2 Full Analysis Set

The **Full Analysis Set (FAS)** is defined as all randomized subjects who have received at least 1 dose of study drug. The FAS 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, unless otherwise specified.

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, unless otherwise specified.

9 STATISTICAL ANALYSIS

9.1 General Considerations

The Schedule of Assessments is provided in Section 3 of the CSP. The precision standards for reporting variables are provided in an internal Biometrics document that specifies the programming rules including the precision for derived variables.

All individual subject data for subjects who were randomized or received at least 1 dose of study drug will be presented in individual subject data listings.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, 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 will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug, unless otherwise specified.

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

Treatment-emergent (TE) Period will include the time from the first dose of study drug in the Treatment Period to either (1) the Safety Follow-up, or (2) the date of the last dose +16 days for subjects who do not have a 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
- In the derivation of maximum and minimum values during the TE period, and maximum and minimum change from baseline values during the 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: Details on how to handle missing data are described in subsequent sections when applicable.

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

Multiplicity: No multiplicity adjustment will be performed for hypothesis testing. All *P* values are nominal.

9.2 Background Characteristics

9.2.1 Subject Disposition

The disposition summary will be provided by treatment and overall.

The number of subjects in the following categories will be summarized:

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

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

- Completed treatment
- Prematurely discontinued treatment and the reason for discontinuation from treatment

- Completed study
- Prematurely discontinued the study and the reason for discontinuation from study

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

9.2.2 Demographics and Baseline Characteristics

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

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 2 or more races reported from a subject])

Baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- BMI category (<18.5, $\geq 18.5 - <25$, $\geq 25 - <30$, ≥ 30 kg/m^2)
- Site (016, 017, 018, 057, 058, 062, 063)
- NPRS at rest
- NPRS category at rest (<8, ≥ 8)
- VRS (moderate, severe)

In addition, data listings will also be provided for:

- Informed consent
- Inclusion/exclusion criteria violations for subjects with any such violations

9.2.3 Medical History

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized descriptively based on the FAS by MedDRA system organ class (SOC) and preferred term (PT). This summary will be provided by treatment group and overall. The corresponding data listing will also be provided.

9.2.4 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary and categorized as the following for the purposes of analysis:

Prior medication: Medication that started before the first dose of study drug, regardless of when dosing of the medication ended

Concomitant medication: Medication continued or newly received on or after the date of the first dose of study drug through the end of the TE Period

A given medication may be classified as a prior medication, a concomitant medication, or both a prior and a concomitant medication.

If a medication start date is on or after the first dose date of study drug, then the medication will be classified as a concomitant medication regardless of whether the medication end date is missing or not. If a medication end date is before the first dose date of study drug, then the medication will be classified as a prior medication regardless of whether the medication start date is missing or not.

Note that a medication that started before the first dose of study drug and continued after the first dose will be classified as a prior medication and separately as a concomitant medication. If a medication has a missing or partially missing start/end date and it cannot be determined whether it was taken before the first dose of study drug, or concomitantly, it will be classified as a prior and a concomitant medication.

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

Prior and concomitant medications will be summarized based on the FAS by Preferred Name and listed. This summary will be provided by treatment group and overall. Supplemental analgesic medications administered after surgery and before randomization will be included in the summary of prior medications but will be listed separately. Rescue medication will also be included in the summary of concomitant medications but will be listed separately.

Prior and concomitant non-pharmacological treatments or procedures will also be listed.

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 the CSP (Table 3-2 and Section 9.6) during a period of 42 hours. Therefore, calculations of exposure to study drug or compliance are not needed. 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

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. IPD rules will be developed and finalized before database lock. IPDs will be identified by the PD review team according to the protocol deviation plan.

IPDs will be summarized descriptively by treatment group and overall.

9.3 Efficacy Analysis

All efficacy analyses described in this section will be based on the FAS, unless specified otherwise. Subjects will be analyzed according to their randomized treatment assignment. All treatment groups will be included in the statistical models described in this section.

9.3.1 Analysis of Primary Endpoint

9.3.1.1 Definition of Primary Endpoint

The primary endpoint is the time-weighted SPID48 at rest ($SPIDr_{0-48}$) after the first dose of study drug. In general, SPIDr is calculated as: $\sum \Delta time_i \times PIDr_i$ where:

- $\Delta time_i$ = time (in hours) elapsed since previous measurement
- $PIDr_i$ = pain intensity (NPRS) at rest at baseline - pain intensity (NPRS) at rest at hour i

Hence:

- $SPIDr_{0-48} = 0.5 \times PIDr_{0.5} + 0.5 \times PIDr_1 + 0.5 \times PIDr_{1.5} + 0.5 \times PIDr_2 + PIDr_3 + PIDr_4 + PIDr_5 + PIDr_6 + 2 \times PIDr_8 + 4 \times PIDr_{12} + 4 \times PIDr_{16} + 4 \times PIDr_{20} + 4 \times PIDr_{24} + 4 \times PIDr_{28} + 4 \times PIDr_{32} + 4 \times PIDr_{36} + 4 \times PIDr_{40} + 4 \times PIDr_{44} + 4 \times PIDr_{48}$

9.3.1.2 Primary Analysis

The primary efficacy analysis will be based on an analysis of covariance (ANCOVA) model. The model will include the $SPIDr_{0-48}$ as the dependent variable and treatment as a fixed effect, with site and baseline NPRS at rest as covariates. Data from all treatment groups will be included in the model. If model estimation does not converge, then site will be removed from the model. The primary results obtained from the model will be the estimated mean treatment effect for VX-548 versus placebo. The Least Squares (LS) mean difference for each dose group of VX-548 versus placebo will be provided along with the 95% CI and 2-sided *P* value. In addition, the LS mean with 95% confidence interval (CI) will be provided for each treatment group.

The following imputation scheme will be applied for the primary analysis:

1) NPRS at rest during the rescue period (within 6 hours after rescue medication) will be replaced by the pre-rescue NPRS at rest.
    - The pre-rescue NPRS at rest will be the NPRS at rest collected immediately before the administration of rescue medication, or the last observed NPRS at rest if that score is missing. The last observed NPRS at rest can be a score from a regularly scheduled measurement at rest or the previous pre-rescue NPRS at rest but cannot be any observed scores during the previous rescue period.
    - If there are multiple administrations of rescue medication within the same 6-hour period, a local highest NPRS at rest will be used for the imputation during the second 6-hour rescue period. The local highest NPRS at rest is the

highest value among the first pre-rescue, the second pre-rescue, and the actual observed (if any) in the overlapping period.

2) Missing NPRS at rest following treatment discontinuation will be imputed with the last observed or previously imputed NPRS at rest prior to discontinuation.
3) Missing NPRS at rest for subjects who completed the treatment but with missing data from certain time point to 48 hours will be imputed with the last observed or previously imputed NPRS at rest.
4) Intermittently missing NPRS at rest will be imputed using linear interpolation.

9.3.1.3 Additional Analyses

This additional analysis will be performed by modifying the primary analysis in such a way that NPRS at rest during the rescue period (within 6 hours after rescue medication) will not be replaced by the pre-rescue NPRS at rest. The observed NPRS at rest will be used instead. The same ANCOVA model as described in Section 9.3.1.2 will be performed.

9.3.1.4 Sensitivity Analyses

This sensitivity analysis will be performed by modifying the primary analysis in such a way that missing NPRS at rest following treatment discontinuation due to an AE will be imputed using the baseline NPRS at rest, while missing NPRS at rest following treatment discontinuation due to other reasons will be imputed by the last observed or previously imputed NPRS at rest prior to discontinuation. The same ANCOVA model as described in Section 9.3.1.2 will be performed.

9.3.1.5 Subgroup Analysis

No subgroup analyses for the primary efficacy variable are planned.

For the primary analysis, additional analysis, and sensitivity analysis, $SPIDr_{0-48}$ will also be summarized descriptively, including standard error (SE), by treatment. In addition, NPRS measurements at rest 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.

9.3.2 Analysis of Secondary Efficacy Variables

9.3.2.1 Definition of Secondary Efficacy Variables

Time-weighted $SPIDr_{0-24}$ after the first dose of study drug: $SPIDr_{0-24}$ is calculated using the following formula:

- $SPIDr_{0-24} = 0.5 \times PIDr_{0.5} + 0.5 \times PIDr_1 + 0.5 \times PIDr_{1.5} + 0.5 \times PIDr_2 + PIDr_3 + PIDr_4 + PIDr_5 + PIDr_6 + 2 \times PIDr_8 + 4 \times PIDr_{12} + 4 \times PIDr_{16} + 4 \times PIDr_{20} + 4 \times PIDr_{24}$

Proportions of subjects with ≥30%, ≥50%, and ≥70% reduction in NPRS at rest at 48 hours after the first dose of study drug: Subjects with ≥30%, ≥50%, and ≥70% reduction in NPRS at rest at 48 hours after the first dose of study drug will be defined as “responders”. The percentage reduction in the NPRS will be calculated as following:

- 100% × (NPRS at rest at baseline − NPRS at rest at 48 hours) / NPRS at rest at baseline

The same imputation strategies as described in Section 9.3.1.2 will be applied. However, subjects who discontinue study drug treatment for any reason prior to 48 hours will be defined as "non-responders" for all 3 criteria.

9.3.2.2 Secondary Analyses

Time-weighted $SPIDr_{0-24}$ after the first dose of study drug: $SPIDr_{0-24}$ will be analyzed in the same way as described in Section 9.3.1.2. $SPIDr_{0-24}$ will also be analyzed in the same way as described for $SPIDr_{0-48}$ in Sections 9.3.1.4 and 9.3.1.5.

Proportions of subjects with ≥30%, ≥50%, and ≥70% reduction in NPRS at rest at 48 hours after the first dose of study drug: The responder rates at 48 hours will be presented descriptively. The Cochran-Mantel-Haenszel test, stratified by the baseline NPRS category at rest (<8, ≥8), will be used to compare responder rates at 48 hours between each dose of VX-548 and placebo.

9.3.3 Analysis of Other Efficacy Variables

9.3.3.1 Definition of Other Efficacy Variables

Time-weighted $SPIDm_{8-24}$ after the first dose of study drug: For the endpoints based on NPRS during movement, SPIDm is calculated as $\sum \Delta time_i \times PIDm_i$ where:

- $\Delta time_i$ = time (in hours) elapsed since previous measurement
- $PIDm_i$ = pain intensity (NPRS) at rest at baseline - pain intensity (NPRS) during movement at hour i

(Note: NPRS at rest at baseline is used because NPRS during movement is not collected at baseline.) $SPIDm_{8-24}$ is calculated using the following formula:

- $SPIDm_{8-24} = 4 \times PIDm_{12} + 4 \times PIDm_{16} + 4 \times PIDm_{20} + 4 \times PIDm_{24}$

Time-weighted $SPIDm_{8-48}$ after the first dose of study drug: $SPIDm_{8-48}$ is calculated using the following formula:

- $SPIDm_{8-48} = 4 \times PIDm_{12} + 4 \times PIDm_{16} + 4 \times PIDm_{20} + 4 \times PIDm_{24} + 4 \times PIDm_{28} + 4 \times PIDm_{32} + 4 \times PIDm_{36} + 4 \times PIDm_{40} + 4 \times PIDm_{44} + 4 \times PIDm_{48}$

Time to onset of "confirmed perceptible pain relief" and "meaningful pain relief" after the first dose of study drug: The time to the onset of "first perceptible pain relief" is the time elapsed from the first dose of study drug until the subject stops the "first perceptible pain relief" stopwatch. The time to the onset of "meaningful pain relief" is the time elapsed from the first dose of study drug until the subject stops the "meaningful pain relief" stopwatch. The time to the onset of "confirmed perceptible pain relief" will be defined as the time to the onset of "first perceptible pain relief" for those subjects who achieved "meaningful pain relief".

If the subject has not stopped the stopwatch by 6 hours after the first dose of the study drug or the subject receives rescue medication during the first 6 hours, the stopwatch will be

stopped and the time to onset will be considered censored at 6 hours. If a time to "first perceptible pain relief" is obtained without subsequent "meaningful pain relief", the time to the onset of "confirmed perceptible pain relief" will also be considered censored at 6 hours.

Proportions of subjects with ≥30%, ≥50%, and ≥70% reduction in NPRS at rest at 24 hours after the first dose of study drug: Subjects with ≥30%, ≥50%, and ≥70% reduction in NPRS at rest at 24 hours after the first dose of study drug will be defined as "responders". The percentage reduction in the NPRS will be calculated as following:

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

The same imputation strategies as described in Section 9.3.1.1 will be applied. However, subjects who discontinue study drug treatment for any reason prior to 24 hours will be defined as "non-responders" for all 3 criteria.

Patient Global Assessment (PGA) of study drug at 48 hours after the first dose of study drug: The PGA of study drug is a single-item assessment of patient perceptions of the method of pain control with the study drug and is evaluated on a 4-point Likert scale (poor, fair, good, or excellent). Subjects with missing PGA at 48 hours will be analyzed as part of a "missing" category.

9.3.3.2 Other Analyses

Time-weighted $SPIDm_{8\text{-}24}$ after the first dose of study drug and time-weighted $SPIDm_{8\text{-}48}$ after the first dose of study drug: $SPIDm_{8\text{-}24}$ and $SPIDm_{8\text{-}48}$ will be analyzed using the same model as described in Section 9.3.1.2, but applying the following imputation strategies. Note: all imputation of NPRS at rest will be performed before any imputation of NPRS during movement.

1) At each administration of rescue medication, a predicted pre-rescue NPRS during movement will be imputed based on the pre-rescue NPRS at rest.
    - The predicted pre-rescue NPRS during movement will be equal to the pre-rescue NPRS at rest (as defined in Section 9.3.1.2) added to Δ_k, a treatment-arm specific adjustment factor. Δ_k is defined as the mean difference between the NPRS during movement and the NPRS at rest among all subjects assigned to treatment arm k, averaged across all timepoints (1) where both NPRS during movement and NPRS at rest are collected, and (2) that are not during any rescue period (within 6 hours after rescue medication).
2) NPRS during movement during the rescue period (within 6 hours after rescue medication) will be replaced by the predicted pre-rescue NPRS during movement defined in Step 1.
    - If there are multiple administrations of rescue medication within the same 6-hour period, a local highest NPRS during movement will be used for the imputation during the second 6-hour rescue period. The local highest NPRS during movement is the highest value among the first predicted pre-rescue NPRS during movement, the second predicted pre-rescue NPRS during

movement, and the actual observed NPRS during movement (if any) in the overlapping period.

3) Missing NPRS during movement at the 8-hour timepoint (i.e., the first scheduled collection of NPRS during movement) will be imputed with a predicted NPRS during movement, calculated by adding Δ_k to the observed or previously imputed NPRS at rest at the 8-hour timepoint, only if no NPRS during movement is available prior to the nominal 8-hour timepoint.
4) Missing NPRS during movement following treatment discontinuation will be imputed with the last observed or previously imputed NPRS during movement prior to discontinuation.
5) Missing NPRS during movement for subjects who completed the treatment but with missing data from a certain time point to 48 hours will be imputed with the last observed or previously imputed NPRS during movement.
6) Intermittently missing NPRS during movement will be imputed using linear interpolation based on observed or previously imputed NPRS during movement.

$SPIDm_{8\text{-}24}$ and $SPIDm_{8\text{-}48}$ will also be summarized descriptively, including standard error (SE), by treatment. In addition, NPRS measurements during movement 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.

Time to onset of "confirmed perceptible pain relief" and "meaningful pain relief" after the first dose of study drug: The time to the onset of "confirmed perceptible pain relief" will be analyzed using a Cox regression model. The model will include treatment as a fixed effect and baseline NPRS at rest as a covariate. Pairwise comparisons between each dose of VX-548 and placebo will be conducted based on this model.

Note: If the placebo group has fewer than 5 subjects experience "confirmed perceptible pain relief", the Cox regression will not be performed. If any other dose group has fewer than 5 subjects experience "confirmed perceptible pain relief", the particular dose group will not be included in the Cox regression model.

Additionally, the Kaplan-Meier method will be used to estimate the median time to onset of "confirmed perceptible pain relief" and the survival curve for each treatment group. Log-rank test will be used to compare curves between the VX-548 dose groups and placebo.

The time to onset of "meaningful pain relief" and the time to the onset of "first perceptible pain relief" will be analyzed in the same way as described for the time to the onset of "confirmed perceptible pain relief".

Proportions of subjects with ≥30%, ≥50%, and ≥70% reduction in NPRS at rest at 24 hours after the first dose of study drug: This variable will be analyzed in the same way as described in Section 9.3.2.2 for NPRS responder rates at 48 hours.

Patient Global Assessment (PGA) of study drug at 48 hours after the first dose of study drug: This variable will be summarized descriptively. The Cochran-Mantel-Haenszel test, stratified

by the baseline NPRS category at rest (<8, ≥8), will be also conducted to compare each VX-548 dose group and placebo.

Percentage of subjects using rescue medication, and total rescue medication usage, 0 to 48 hours after the first dose of study drug: The percentage of subjects using rescue medication during 0-48 hours will be analyzed using the Cochran-Mantel-Haenszel test, stratified by the baseline NPRS category at rest (<8, ≥8), to compare each VX-548 dose group and placebo. The total rescue medication usage from 0 to 48 hours will be summarized descriptively, and the Wilcoxon rank-sum test, stratified by the baseline NPRS category at rest (<8, ≥8), will be conducted to compare each VX-548 dose group and placebo.

All analyses described in Sections 9.3.1, 9.3.2 and 9.3.3 for comparisons between VX-548 and placebo will be repeated for comparisons between HB/APAP and placebo.

9.4 Safety Analysis

The overall safety profile of VX-548 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, and urinalysis)
- ECG outcomes
- Vital signs

All safety analyses will be performed based on the Safety Set based on actual treatment. In the unexpected scenario that a subject may receive more than one treatment in the study, the following algorithm will be used to define the actual treatment: regardless of the subject's randomized treatment assignment, if the subject received any VX-548 treatment, the actual treatment is defined as the highest dose level among all received VX-548 treatment; if the subject did not receive any VX-548 treatment but did receive HB/APAP during at least one visit, the actual treatment is defined as HB/APAP; the actual treatment is defined as placebo only if the subject received placebo at all visits in the study.

Only descriptive analyses of safety will be performed, and no statistical hypothesis testing will be performed.

9.4.1 Adverse Events

AEs will be coded according to MedDRA. For analysis purposes, AEs will be classified as pretreatment AEs and TEAEs as follows:

Pretreatment AEs: AEs that occurred before the first dose of study drug

Treatment-emergent AEs: AEs that worsened or started on or after the first dose date of study drug through the end of the TE Period

For AEs with completely missing or partial start dates, if there is no clear evidence that the AEs started before or after the first dose of study drug, the AEs will be classified as TEAEs.

Imputation rules for missing or partial AE start dates are defined in Appendix C.

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

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Related TEAEs
- Serious TEAEs
- Related serious TEAEs
- TEAEs leading to death

Summaries will be presented by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Only the maximum severity level will be presented in the severity summaries, and the strongest relationship level in the relationship summaries.

All AEs, including pretreatment AEs and TEAEs will be presented in an individual subject data listing based on the All Subjects Set. In addition, a listing containing individual subject adverse event data for TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, SAEs and all deaths will be provided separately.

9.4.2 Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using SI units. For treatment-emergent laboratory measurements, the observed values and change from baseline values of the continuous hematology, chemistry, and coagulation results will be summarized at each visit.

The number and percentage of subjects with selected test values meeting threshold analysis criteria during the TE period will be summarized. The threshold analysis criterion shift from baseline will also be summarized for chemistry measurements. The threshold analysis criteria are provided in Appendix D.

In addition, listings of individual subject hematology, chemistry, and coagulation values outside the normal reference ranges will be provided. These listings will include data from both scheduled and unscheduled visits.

Results of urinalysis and urine/serum pregnancy tests will be in individual subject data listings only.

9.4.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided at each visit and time point, as applicable, for the following ECG measurements: heart rate (HR; beats per minute [bpm]), PR interval (msec), RR interval (msec), QRS duration (msec), QT interval (msec), and QT interval corrected for HR intervals (QTcF [msec]). In addition, the number and percentage of subjects by maximum treatment-emergent 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 treatment-emergent change from baseline value of QT/QTcF intervals, categorized ≤0 msec, and >0 and ≤30 msec, >30 and ≤60 msec, and >60 msec, will be provided.

The number and percentage of subjects meeting threshold analysis criteria during the TE period will be summarized. The threshold analysis criteria are provided in Appendix D. A listing containing individual subject measurements meeting the threshold value criteria at any time point will be provided. This listing will include data from both scheduled and unscheduled visits.

9.4.4 Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized at each visit. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), pulse rate (beats per minute), body temperature (°C), respiratory rate (breaths per minute), and oxygen saturation (%).

The number and percentage of subjects meeting threshold analysis criteria during the TE Period will be summarized. The threshold analysis criteria are provided in Appendix D.

In addition, a listing containing individual subject vital signs values will be provided. This listing will include data from both scheduled and unscheduled visits.

9.4.5 Physical Examination

Physical examination (PE) results will be presented in an individual subject data listing only.

10 SUMMARY OF INTERIM AND IDMC ANALYSES

Not applicable.

11 REFERENCES

Not applicable.

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/Timepoint[1]	Target Study Day /Timepoint per the protocol	Analysis Visit Window (in study days/ timepoints) [2, 3, 4, 5]
Safety Assessment			
Hematology Serum Chemistry Coagulation	Baseline	Day 1 (Procedure through randomization/ predose)	≤ Day 1 predose
	48 hours	48 hours	Nominal visit
Standard 12-Lead ECG	Baseline	Day 1 (Procedure through randomization/ predose)	≤ Day 1 predose
	4 hours	4 hours	Nominal visit for all visits
	16 hours	16 hours	
	28 hours	28 hours	
	40 hours	40 hours	
Vital Signs	Baseline	Day 1 (Procedure through randomization/ predose)	≤ Day 1 predose
	2 hours	2 hours	Nominal visit for all visits
	4 hours	4 hours	
	24 hours	24 hours	
	48 hours	48 hours	
	Safety Follow-up	Not applicable	
Efficacy Assessment			
NPRS at rest	Baseline	Day 1 (Procedure through randomization/ predose)	≤ Day 1 predose
	At 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours	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 for 0.5 to 48 hours
NPRS during movement	At 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours	At 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours	± 5 minutes for 8 to 48 hours

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

Assessment	Visit/Timepoint[1]	Target Study Day /Timepoint per the protocol	Analysis Visit Window (in study days/ timepoints) [2, 3, 4, 5]
VRS	Baseline	Day 1 (Procedure through randomization/ predose)	≤ Day 1 (Procedure through randomization/predose)
Rescue Medication	N/A	N/A	[Day 1 post-dose, 48 hours post-dose]

Notes:
[1] Visit/Timepoint name for analysis purposes is used to report data in tables and figures.

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

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

b. If there is more than 1 numerical measurement available within the same visit window, use the following rules:

   i. The measurement closest to the target day/time point will be used.

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

   iii. If a scheduled and an unscheduled measurement have the same date/time, the unscheduled measurement will be used.

[3]For measurements collected on the date of first dose of study drug in Treatment Period, if it cannot be determined whether the measurement is before or after the first dose:

a. If a scheduled measurement is pre-dose in the CSP, it will be treated as a pre-dose observation. If a scheduled measurement is post-dose in the CSP, it will be treated as a post-dose observation.

b. Unscheduled measurements will be treated as post-dose observations.

[4]When defining baseline for efficacy and safety, refer to the generic baseline definition in Section 9.1.

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

Missing or partial dates will be imputed for medications. 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 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 times, only use the imputed start date to categorize as 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 as prior and/or concomitant medication. Imputation of missing and/or partial dates for non-pharmacological treatments/procedures will follow the same imputation rules.

Table 12-2 Prior and/or Concomitant Categorization of a Medication

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

C: Concomitant; P: Prior

Appendix C: Imputation Rules for Missing AE Dates and Times

Imputation rules for missing or partial AE start dates and times 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 a pretreatment AE.
- If the AE start date is on or after the first dose date, the AE will be classified as a TEAE.

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 the 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 the TE period to determine whether the AE is a pretreatment AE or TEAE.

If Day and Month of AE start date are missing:

- If AE start year is the same as the year of the first dose date, then:
  - If the full (or partial) AE end date is NOT before the first dose date or the AE end date is missing, then impute the AE start month and day as the month and day of the 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 a 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 the site with no imputation. 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 a 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 a pretreatment AE.
- If the AE start date is on or after the first dose date, the AE will be classified as a TEAE.

A missing or partially missing AE end date will not be imputed.

Appendix D: Threshold Value Criteria

Table 12-1 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Clinical Chemistry		
ALT	>ULN - ≤3xULN >3x - ≤5xULN >5x - ≤8xULN >8x - ≤20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
AST	>ULN - ≤3xULN >3x - ≤5xULN >5x - ≤8xULN >8x - ≤20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
ALT or AST	(ALT>ULN - ≤ 3xULN) or (AST>ULN - ≤3xULN) (ALT>3x - ≤5xULN) or (AST>3x - ≤5xULN) (ALT>5x - ≤8xULN) or (AST>5x - ≤8xULN) (ALT>8x - ≤20xULN) or (AST>8x - ≤20xULN) ALT>20xULN or AST>20xULN	FDA DILI Guidance Jul 2009.
Alkaline Phosphatase	>ULN - ≤1.5xULN >1.5 - ≤2.5xULN >2.5 - ≤5.0xULN >5.0 - ≤20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>ULN - ≤1.5xULN >1.5 - ≤2xULN >2 - ≤3xULN >3 - ≤10xULN >10xULN	FDA DILI Guidance Jul 2009.
Direct Bilirubin	>ULN - ≤1.5xULN >1.5 - ≤2xULN >2 - ≤3xULN >3 - ≤10xULN >10xULN	FDA DILI Guidance Jul 2009.
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	FDA DILI Guidance Jul 2009.

Table 12-1 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
GGT	>ULN - ≤2.5xULN >2.5 - ≤5.0xULN >5.0 - ≤20.0xULN >20.0xULN	CTCAE grade 1-4
Albumin	<LLN - ≥30 g/L <30 - ≥20 g/L <20 g/L	CTCAE grade 1-3
Creatinine	>ULN - ≤1.5xULN >1.5 - ≤3.0xULN >3.0 - ≤6.0xULN >6.0xULN	CTCAE grades 1-4
Lipase	>ULN - ≤1.5xULN >1.5 - ≤2xULN >2 - ≤5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
Creatine kinase	>ULN - ≤2.5xULN >2.5 - ≤5xULN >5 - ≤10xULN >10xULN	CTCAE grades 1-4
Hematology		
Hemoglobin	Hgb decreased (anemia) <LLN - ≥100 g/L <100 - ≥80 g/L <80 g/L	CTCAE grade 1-3
	Hgb increased >ULN - ≤20 g/L above ULN >20 g/L above ULN - ≤40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3
Platelets	Platelet decreased <LLN - ≥75.0 x 10e9 /L <75.0 - ≥50.0 x 10e9 /L <50.0 - ≥25.0 x 10e9 /L <25.0 x 10e9 /L	CTCAE grade 1-4
	Platelet increased >ULN	No CTCAE available
Coagulation		
Activated partial thromboplastin time (PTT)	>ULN - ≤1.5xULN >1.5 - ≤2.5xULN >2.5xULN	CTCAE grade 1-3

Table 12-1 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤1.5xULN >1.5 - ≤2.5xULN >2.5xULN	CTCAE grade 1-3

Table 12-2 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
HR	Bradycardia <50 bpm <45 bpm Decrease from baseline ≥10 bpm Decrease from baseline ≥20 bpm <50 bpm and decrease from baseline ≥10 bpm <50 bpm and decrease from baseline ≥20 bpm	Per HV grade 2, 3, plus shift change
	Tachycardia >100 bpm >115 bpm >130 bpm Increase from baseline ≥10 bpm Increase from baseline ≥20 bpm >100 bpm and increase from baseline ≥10 bpm >100 bpm and increase from baseline ≥20 bpm	Per HV grade 1, 2, 3, plus shift change
PR	≥240 ms ≥300 ms ≥200 ms and increase from baseline ≥40 ms ≥200 ms and increase from baseline ≥100 ms	
QRS	>110 ms >160 ms Increase from baseline ≥20 ms Increase from baseline ≥40 ms	
QTc	>450 to <500ms (Male) or >470 to <500ms (Female) ≥500 ms Increase from baseline Increase from baseline >10 ms Increase from baseline >20 ms Increase from baseline >40 ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula.

Table 12-3 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
Pulse Rate	Same as above in ECG category	
SBP increased	>140 mmHg >160 mmHg >10 mmHg increase from baseline >20 mmHg increase from baseline >140 mmHg & >10 mmHg increase from baseline >140 mmHg & >20 mmHg increase from baseline >160 mmHg & >10 mmHg increase from baseline >160 mmHg & >20 mmHg increase from baseline	
SBP decrease	<90 mmHg <80 mmHg >10 mmHg decrease from baseline >20 mmHg decrease from baseline <90 mmHg and >10 mmHg decrease from baseline <90 mmHg and >20 mmHg decrease from baseline <80 mmHg and >10 mmHg decrease from baseline <80 mmHg and >20 mmHg decrease from baseline	Per HV grade 1, 3, plus shift change
DBP increased	>90 mmHg >100 mmHg >5 mmHg increase from baseline >10 mmHg increase from baseline >90 mmHg and >5 mmHg increase from baseline >90 mmHg and >10 mmHg increase from baseline >100 mmHg and >5 mmHg increase from baseline >100 mmHg and >10 mmHg increase from baseline	
DBP decreased	<60 mmHg <45 mmHg >5 mmHg decrease from baseline >10 mmHg decrease from baseline <60 mmHg and >5 mmHg decrease from baseline <60 mmHg and >10 mmHg decrease from baseline <45 mmHg and >5 mmHg decrease from baseline <45 mmHg and >10 mmHg decrease from baseline	
Oxygen saturation decreased	<88% <95% and decrease from baseline >5% of absolute oxygen saturation	