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VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX22-548-104 (Final Analysis)

A Phase 3, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of VX-548 for Acute Pain After a Bunionectomy

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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 VX22-548-104 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 data 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 data lock will be documented in the clinical study report for this study.

Analyses 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 Vertex Clinical Pharmacology department.

5 STUDY OBJECTIVES

5.1 Primary Objective

- To evaluate the efficacy of VX-548 in treating acute pain after a bunionectomy

5.2 Secondary Objectives

- To evaluate the safety and tolerability of VX-548

5.3 Other Objectives

- To evaluate the pharmacokinetics 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 the numeric pain rating scale (NPRS) from 0 to 48 hours (SPID48) compared to placebo

6.2 Secondary Endpoints

6.2.1 Key Secondary Endpoints

- SPID48 compared to hydrocodone bitartrate/acetaminophen (HB/APAP)
- Time to ≥2-point reduction in NPRS from baseline compared to placebo

6.2.2 Other Secondary Endpoints

- Time to ≥1-point reduction in NPRS from baseline compared to placebo

- Proportion of subjects reporting good or excellent on the Patient Global Assessment (PGA) at 48 hours compared to placebo
- Incidence of vomiting or nausea compared to HB/APAP
- Time-weighted SPID as recorded on the NPRS from 0 to 24 hours (SPID24) compared to placebo
- Time to first use of rescue medication compared to placebo
- Proportion of subjects using rescue medication from 0 to 48 hours compared to placebo
- Total rescue medication usage from 0 to 48 hours compared to placebo
- 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 the NPRS from 0 to 36 hours (SPID36) compared to placebo
- Time-weighted SPID as recorded on the NPRS from 0 to 12 hours (SPID12) compared to placebo
- Proportion of subjects with ≥30% reduction in NPRS at 48 hours compared to placebo
- Proportion of subjects with ≥50% reduction in NPRS at 48 hours compared to placebo
- Proportion of subjects with ≥70% reduction in NPRS at 48 hours compared to placebo
- Proportion of subjects using rescue medication from 0 to 24 hours compared to placebo
- Time to first use of rescue medication in the first 12 hours compared to placebo
- Proportion of subjects using rescue medication from 0 to 12 hours compared to placebo
- Proportion of subjects using rescue medication from 24 to 48 hours compared to placebo
- PK parameter estimates of VX-548 and its metabolite, [redacted]

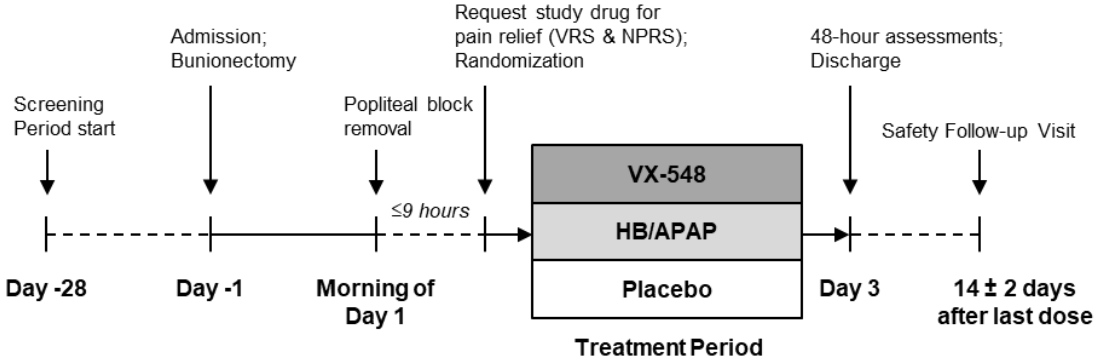
7 OVERALL DESIGN

This is a Phase 3, randomized, double-blind, placebo-controlled, 3-arm, parallel study design evaluating the efficacy and safety of VX-548 in treating acute pain after a bunionectomy (Figure 7-1).

On Day -1, subjects will undergo a primary unilateral bunionectomy with distal first metatarsal osteotomy (i.e., Austin procedure) and internal fixation under regional anesthesia (Mayo and popliteal sciatic block). A continuous popliteal sciatic block infusion (0.2% ropivacaine) will be started after surgery and remain in place until approximately 3AM, but no later than 5AM, on Day 1. After removal of the popliteal sciatic block, a subject will be randomized to 1 of 3 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, and (3) the subject's

pain is ≥4 on the NPRS. If a subject does not meet the VRS and NPRS criteria within 9 hours of removal of the popliteal sciatic block, the subject will not be eligible for this study.

Figure 7-1 VX22-548-104 Study Design



HB/APAP: hydrocodone bitartrate/acetaminophen; NPRS: numeric pain rating scale; VRS: verbal categorical rating scale

Notes: After removal of the popliteal sciatic block, a subject will be randomized to 1 of 3 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, and (3) the subject's pain is ≥4 on the NPRS. If a subject does not meet the VRS and NPRS criteria within 9 hours after removal of the popliteal sciatic block, the subject will not be eligible for this study. Figure is not drawn to scale.

Approximately 1000 subjects will be randomized 2:2:1 to 3 treatment groups: VX-548 (100 mg first dose, then 50 mg every 12 hours [q12h]); HB/APAP (5 mg/325 mg every 6 hours [q6h]; opioid reference); or placebo (Table 7-1). Randomization will be stratified by site and baseline NPRS (<8 versus ≥8). To maintain the blind, all subjects will receive the same number of tablets and capsules q6h in a double-dummy design.

Table 7-1 VX22-548-104 Treatment Groups

Treatment	Active Dose	Number of Subjects
VX-548	100 mg first dose, then 50 mg q12h	400
HB/APAP	5 mg/325 mg q6h	400
Placebo	--	200

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 capsules in a double-dummy design. VX-548 active or VX-548 placebo tablets will be administered to all subjects q12h as follows: 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 capsules will be administered to all subjects q6h as follows: 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 on the NPRS at each scheduled time point 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.

Ibuprofen (400 mg orally q6h as needed [prn]) 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 receive rescue medication, and subjects should generally not receive rescue medication unless their NPRS is ≥4.

7.1 Sample Size and Power

Assuming a standardized effect size of 0.40 for VX-548 compared to placebo and 0.25 for VX-548 compared to HB/APAP, 338 evaluable subjects per group for VX-548 and HB/APAP and 169 evaluable subjects for placebo will provide more than 90% power for the primary endpoint of VX-548 versus placebo on SPID48 and 90% power for the key secondary endpoint of VX-548 versus HB/APAP on SPID48, based on 2-sample *t*-tests with significance level 0.05. To allow about 15% dropout, a total of approximately 1000 subjects are planned to be enrolled.

7.2 Randomization

Refer to Section 9.2 of the CSP for details.

7.3 Blinding and Unblinding

Refer to Section 10.8 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 the disposition summary table, unless otherwise specified.

8.2 Full Analysis Set

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

8.3 Safety Set

The **Safety Set** is defined as all subjects who have received at least 1 dose of study drug. The Safety Set is to be used for all safety analyses in which subjects will be analyzed according to the treatment they received.

9 STATISTICAL ANALYSIS

9.1 General Considerations

The Schedule of Assessments is provided in Section 3 of 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.

For ECGs, the baseline value will be defined as the average of the most recent non-missing measurements (scheduled or unscheduled) collected before the first dose of study drug, expected to be the triplicate predose measurements on Day 1.

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 the Safety Follow-up Visit or to the completion of study participation (as defined in Section 9.1.6 of the CSP), whichever occurs first.

Unscheduled visits: Unscheduled visit measurements will be included in the 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.

Multiplicity: The multiplicity adjustment procedure for the primary and key secondary endpoints is described in Section 9.3.2.2. All other *P* values are nominal.

9.2 Background Characteristics

9.2.1 Subject Disposition

The disposition summary will be provided by treatment group and overall.

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

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

- Safety Set
- Randomized but not dosed

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 disposition listing and a randomization listing of subjects will 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 at screening (in years)
- Age at screening category (≥18 to <65, ≥65)
- 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)
- Site
- NPRS
- NPRS category (<8, ≥8)
- VRS (moderate, severe)

In addition to demographic data and baseline characteristics, data listings will also be provided for:

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

9.2.3 Medical History

Medical history will be coded 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 after the date and time 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/time is on or after the first dose of study drug, then the medication will be classified as a concomitant medication regardless of whether the medication end date/time is missing. If a medication end date/time is before the first dose of study drug, then the medication will be classified as a prior medication regardless of whether the medication start date/time is missing.

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 or end date/time 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/end 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. Pre- and intra-operative medications will be included in the summary of prior medications and will be listed separately. Similarly, supplemental analgesic medications administered after surgery and before removal of the popliteal sciatic block will be included in the summary of prior medications and will also be summarized and listed separately. Concomitant analgesic medications will be included in the summary of concomitant medications and will be listed separately. Rescue medication will be included in the summary of concomitant medications and 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 compliance are not needed.

Study drug exposure will be summarized descriptively by treatment group in terms of the total number of tablets (VX-548 or placebo) and total number of capsules (HB/APAP or placebo) administered. Separate exposure summaries will be planned based on the Safety Set and the FAS.

All data collected during dispensation of study drug (e.g., time of administration and number of tablets/capsules taken) will be presented in an individual data listing.

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, as well as presented in an individual data listing.

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.

9.3.1 Analysis of Primary Endpoint

9.3.1.1 Definition of Primary Endpoint

The primary endpoint is SPID48 compared to placebo. In general, SPID is calculated as: $\sum(t_{i-1} - t_i) \times PID_{t_i}$ where:

- t_i = scheduled time since first dose (in hours) for time point i ($t_0 = 0$ hours; $t_1 = 0.5$ hour, etc.)
- PID_{t_i} = pain intensity (NPRS) at time point i - pain intensity (NPRS) at baseline

Hence:

- SPID48 = -(0.5 × $PID_{0.5}$ + 0.5 × PID_1 + 0.5 × $PID_{1.5}$ + 0.5 × PID_2 + PID_3 + PID_4 + PID_5 + PID_6 + 2 × PID_8 + 4 × PID_{12} + 4 × PID_{16} + 4 × PID_{20} + 4 × PID_{24} + 4 × PID_{28} + 4 × PID_{32} + 4 × PID_{36} + 4 × PID_{40} + 4 × PID_{44} + 4 × PID_{48})

In this definition of SPID48, a higher value of SPID48 indicates greater pain reduction from baseline.

9.3.1.2 Definition of Primary Estimand

The primary estimand is defined as the following:

- Treatment: VX-548 versus placebo
- Population: Study population meeting the study inclusion and exclusion criteria
- Variable: SPID48

- Handling of intercurrent events:
    - The hypothetical strategy will be used to handle the use of rescue medication, which means that the observed NPRS scores during the rescue period will not be used and will instead be replaced by imputed values.
    - The hypothetical strategy will be used to handle treatment discontinuation, which means that missing NPRS scores after treatment discontinuation will be imputed.
- Population level summary: Difference in variable means

9.3.1.3 Primary Analysis

The primary analysis for the primary estimand will be based on an analysis of covariance (ANCOVA) model. The model will include SPID48 as the dependent variable and treatment as a fixed effect, with site and baseline NPRS as covariates. If model estimation does not converge, then site will be removed from the model. The Least Squares (LS) mean difference for VX-548 versus placebo will be provided along with the SE, 95% confidence interval (CI) and 2-sided *P* value. In addition, the LS mean with SE and 95% CI will be provided for each treatment group. Analogous results for HB/APAP versus placebo will be reported as well.

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

1) NPRS scores during the rescue period (within 6 hours after rescue medication) will be replaced by the pre-rescue NPRS score.
    - The pre-rescue NPRS score will be the NPRS score collected immediately before the administration of rescue medication, or the previous NPRS score if that score is missing. The previous NPRS score can be a score from a regularly scheduled measurement or the previous pre-rescue NPRS score but cannot be any observed score during the previous rescue period.
    - If there are multiple administrations of rescue medication leading to overlapping rescue periods, the pre-rescue NPRS score for the first rescue period will replace all NPRS scores from the start of the first rescue period through the end of the last overlapping rescue period (i.e., 6 hours after the corresponding use of rescue medication).
2) Missing NPRS scores following treatment discontinuation due to an AE will be imputed using the baseline NPRS score; missing NPRS scores following treatment discontinuation due to other reasons will be imputed with the last NPRS score prior to discontinuation.
3) Missing NPRS scores for subjects who completed the treatment but with missing data from a certain time point to 48 hours will be imputed with the last NPRS score.
4) Intermittently missing NPRS scores will be imputed using linear interpolation.

In addition, NPRS scores and change from baseline in NPRS scores (i.e., pain intensity difference) will be summarized descriptively, including SE, by treatment group at each scheduled time point. The mean NPRS scores and SEs over time by treatment group, as well

as the mean pain intensity differences and SEs over time by treatment group, will be presented in separate figures.

9.3.1.5 Subgroup Analysis

Subgroup analyses of the primary efficacy endpoint will be performed for age, sex and race according to the following categories. The analyses will be performed using the same imputation scheme and the same ANCOVA model as in Section 9.3.1.3:

- Age at screening (≥18 to <65, ≥65)
- Sex (male, female)
- Race (White, Non-White)

Each of these subgroup analyses will only be performed if ≥10% of subjects in the FAS are members of both subgroups.

9.3.2 Analysis of Key Secondary Efficacy Variables

9.3.2.1 Definitions and Analysis Methods

SPID48 compared to HB/APAP: SPID48 is defined the same way as in Section 9.3.1.1.

The estimand for SPID48 compared to HB/APAP is identical to the primary estimand described in Section 9.3.1.2 except that the treatment attribute is VX-548 versus HB/APAP.

SPID48 compared to HB/APAP will be analyzed using the same imputation scheme and model as for the primary analysis (as described in Section 9.3.1.3). The LS mean difference for VX-548 versus HB/APAP will be provided along with the 95% CI and 2-sided *P* value.

Time to ≥2-point reduction in NPRS from baseline compared to placebo: Time to ≥2-point reduction in NPRS from baseline is the time elapsed from the first dose of study drug until the first time the subject has at least a 2-point reduction in the NPRS from baseline. Subjects who have not reached at least a 2-point reduction in NPRS from baseline by 48 hours will be censored at 48 hours.

The estimand for the time to ≥2-point reduction in NPRS from baseline is defined as the following:

- Treatment: VX-548 versus placebo
- Population: Study population meeting the study inclusion and exclusion criteria
- Variable: Time to ≥2-point reduction in NPRS from baseline
- Handling of intercurrent events: Same as the primary estimand, with the hypothetical strategy applied to handle rescue medication use and treatment discontinuation
- Population level summary: Medians of the variable for each treatment group

This endpoint will be calculated based on NPRS scores collected at scheduled time points (using the same imputation scheme as described in Section 9.3.1.3). The Kaplan-Meier method will be used to estimate the median time and the survival curve for each treatment group. A log-rank test will be used to compare the survival curves between VX-548 and placebo. The median time along with the 95% CI for each treatment group from the Kaplan-Meier analysis and the *P* value for the comparison to placebo from the log-rank test will be provided.

9.3.2.2 Multiplicity Adjustment

A hierarchical testing procedure will be used to control the overall type 1 error at a significance level of 0.05 for the primary endpoint and the key secondary endpoints tested. For a test at any step to be considered statistically significant within the testing hierarchy, that test and all previous tests (if any) within the hierarchy must be statistically significant at the 0.05 level. The testing order of the primary and key secondary endpoints is as follows:

- SPID48 compared to placebo
- SPID48 compared to HB/APAP
- Time to ≥2-point reduction in NPRS from baseline compared to placebo

9.3.3 Analysis of Other Secondary Efficacy Variables

Time to ≥1-point reduction in NPRS from baseline compared to placebo: Time to ≥1-point reduction in NPRS from baseline is the time elapsed from the first dose of study drug until the first time the subject has at least a 1-point reduction in the NPRS from baseline. Subjects who have not reached at least a 1-point reduction in NPRS from baseline by 48 hours will be censored at 48 hours. This variable will be analyzed the same way as described in Section 9.3.2.1 for the time to ≥2-point reduction in NPRS from baseline.

Proportion of subjects reporting good or excellent on the PGA at 48 hours compared to placebo: 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 who discontinue study drug treatment for any reason prior to 48 hours and subjects with missing PGA at 48 hours will be considered as non-responders (i.e., not reporting good or excellent on the PGA). This variable will be summarized

descriptively, and the Cochran-Mantel-Haenszel test, stratified by the baseline NPRS category (<8, ≥8), will be conducted to compare VX-548 and placebo.

Incidence of vomiting or nausea compared to HB/APAP: This endpoint will be analyzed based on the Safety Set. The incidence of vomiting or nausea is the proportion of subjects reporting the treatment-emergent adverse events of vomiting or nausea from the first dose of study drug through completion of study participation. When computing these proportions, subjects with multiple occurrences of either event will be counted once. Subjects who experience both vomiting and nausea will only be counted once. This variable will be summarized descriptively, and Pearson's chi-squared test will be conducted to compare VX-548 and HB/APAP. If any expected counts are <5, Fisher's exact test will be used instead.

SPID24 compared to placebo: SPID24 is calculated using the following formula:

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

SPID24 will be analyzed in the same way as described in Section 9.3.1.3 for the primary endpoint.

Time to first use of rescue medication compared to placebo: Time to first use of rescue medication is the time from the first dose of study drug until the first use of rescue medication. Subjects who do not take any rescue medication within 48 hours will be censored at 48 hours. The Kaplan-Meier method will be used to estimate the median time to first use of rescue medication and the survival curve for each treatment group. A log-rank test will be used to compare the survival curves between VX-548 and placebo. The median time to first use of rescue medication along with the 95% CI for each treatment group from the Kaplan-Meier analysis and the *P* value for the comparison to placebo from the log-rank test will be provided.

Proportion of subjects using rescue medication from 0 to 48 hours compared to placebo: This variable will be summarized descriptively, and the Cochran-Mantel-Haenszel test, stratified by the baseline NPRS category (<8, ≥8), will be conducted to compare VX-548 and placebo.

Total rescue medication usage from 0 to 48 hours compared to placebo: This variable will be summarized descriptively, and the Wilcoxon rank-sum test, stratified by the baseline NPRS category (<8, ≥8), will be conducted to compare VX-548 and placebo.

[redacted]

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 receives more than one treatment in the study, the following algorithm will be used to define actual treatment: for any dosed subjects, the actual treatment is defined as VX-548 if the subject received any VX-548 treatment, regardless of the randomized treatment assignment; the actual treatment is defined as HB/APAP if the subject did not receive any VX-548 treatment but did receive any HB/APAP; the actual treatment is defined as placebo only if the subject received placebo on all dosing occasions.

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 at or after the first dose of study drug through the end of the TE Period

For AEs with completely missing or partial start dates/times, 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/times are defined as Appendix C.

AE summary tables will be presented only for TEAEs by treatment group, 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, and 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. In addition, listings containing individual subject AE 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 number and percentage of subjects with shift from baseline in selected test values meeting threshold analysis criteria will also be summarized for chemistry measurements. The threshold analysis criteria are provided in Appendix D.

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

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.

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 corrected for HR intervals (QTcF [msec]).

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.

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 as ≤0 msec, and >0 and ≤30 msec, >30 and ≤60 msec, and >60 msec, will be provided.

ECGs are performed in triplicate. The mean of the ECG measurements will be used as the ECG value for summaries of observed values and change from baseline values. All reported ECG measurements will be used to conduct threshold analyses and to assess maximum treatment-emergent values.

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/Time point[1]	Target Study Day /Time point per the protocol	Analysis Visit Window (in study days/time points) [2, 3, 4]
Safety Assessment			
Hematology Serum Chemistry Coagulation	Baseline 48 hours	Day 1 48 hours	≤ Day 1 predose Nominal visit
Standard 12-Lead ECG	Baseline 4 hours 14 hours 26 hours 38 hours	Day 1 4 hours 14 hours 26 hours 38 hours	≤ Day 1 predose Nominal visit for all visits
Vital Signs	Baseline 2 hours 4 hours 24 hours 48 hours Safety Follow-up	Day 1 2 hours 4 hours 24 hours 48 hours Not applicable	≤ Day 1 predose Nominal visit for all visits
Efficacy Assessment			
NPRS	Baseline At 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours	Day 1 At 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours	≤ Day 1 predose ± 10 minutes for 0.5 to 2 hours ± 15 minutes for 3 to 8 hours ± 30 minutes for 12 to 48 hours
VRS	Baseline	Day 1	≤ Day 1 predose
Rescue Medication	N/A	N/A	[Day 1 post-dose, 48 hours]

Notes:
[1] Visit/time point names for analysis purposes are 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; or

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

[3]For measurements collected on the date of the first dose of study drug, 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 Medication and Dates/Times

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 and time:
    a. If hour and/or minute are missing, do not impute.
    b. If day is missing, use the last day of the month.
    c. If day and month are both missing, use the last day of the year.
    d. 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 the prior and/or concomitant medication as described in Table 12-2. If hour and/or minute of the first dose time are missing, only use the first dose date to categorize the prior and/or concomitant medication. Imputation of missing and/or partial dates for non-pharmacological treatments/procedures will follow the same imputation rule.

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

	Medication Stop Date	
Medication Start Date	**< First Dose Date/Time of Study Drug**	**≥ First Dose Date/Time and ≤ End Date of TE Period**
< First dose date/time of study drug	P	PC
≥ First dose date/time 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 12-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Clinical Chemistry		
ALT	>ULN - ≤3xULN >3x - ≤5xULN >5x - ≤8xULN >8x - ≤20xULN >20xULN	FDA DILI Guidance Jul 2009.
AST	>ULN - ≤3xULN >3x - ≤5xULN >5x - ≤8xULN >8x - ≤20xULN >20xULN	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 - ≤5xULN >5 - ≤20xULN >20xULN	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 12-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
GGT	>ULN - ≤2.5xULN >2.5 - ≤5xULN >5 - ≤20xULN >20xULN	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 - ≤3xULN >3 - ≤6xULN >6xULN	CTCAE grades 1-4
Lipase	>ULN - ≤1.5xULN >1.5x - ≤2xULN >2x - ≤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 12-3 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 >2.5 x ULN	CTCAE grade 1-3

Table 12-4 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 12-5 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	