1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX24-548-113

A Phase 4, Open-label, Single-arm Study Evaluating the Effectiveness and Safety of Suzetrigine as Part of Multimodal Therapy for Acute Pain After Aesthetic or Reconstructive Surgeries

[redacted]

Date of SAP: 28 May 2025 (v1.0)

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2 TABLE OF CONTENTS

1 Title Page 1
2 Table of Contents 2
3 Modifications 4
3.1 Modifications to the Approved Clinical Study Protocol 4
3.2 Modifications to the Approved Statistical Analysis Plan 4
4 Introduction 5
5 Study Objectives 5
5.1 Primary Objective 5
[redacted]
6 Study Endpoints 5
6.1 Primary Endpoint 5
[redacted]
7 Overall Design 6
7.1 Sample Size and Power 8
7.2 Randomization 8
7.3 Blinding and Unblinding 8
8 Analysis Sets 8
8.1 All Subjects Set 8
8.2 Modified Full Analysis Set 8
8.3 Safety Set 8
8.4 Interim All Subjects Set 8
8.5 Interim Full Analysis Set 8
8.6 Interim Safety Set 8
9 Statistical Analysis 9
9.1 General Considerations 9
9.2 Background Characteristics 9
9.2.1 Subject Disposition 9
9.2.2 Demographics and Baseline Characteristics 10
9.2.3 Medical History 11
9.2.4 Prior and Concomitant Medications 11
9.2.5 Study Drug Exposure 11
9.2.6 Important Protocol Deviations 11
9.3 Effectiveness Analysis 11
9.3.1 Analysis of Primary Endpoint 12
[redacted]
9.4 Safety Analysis 13
9.4.1 Adverse Events 13
9.4.2 Clinical Laboratory Assessments 14
9.4.3 Electrocardiogram 14
9.4.4 Vital Signs 15
9.4.5 Physical Examination 15
10 Summary of Interim Analyses 15
11 References 16
12 List of Appendices 17

Appendix A: Analysis Visit Windows for Effectiveness and Safety Assessments 17
Appendix B: Imputation Rules for Missing Medication Information..... 18
[redacted]
Appendix D: Imputation Rules for Missing AE Dates and Times..... 20
Appendix E: Threshold Value Criteria 21

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 effectiveness and safety endpoints defined in the study protocol of VX24-548-113 and provides additional details and clarifications.

Vertex will perform the final statistical analysis of the effectiveness 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 any interim analysis data cut, and before the clinical database lock. 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.

5 STUDY OBJECTIVES

5.1 Primary Objective

- To evaluate the effectiveness of Suzetrigine (SUZ) as part of Multimodal Therapy (MMT) in treating acute postoperative pain

[redacted]

6 STUDY ENDPOINTS

6.1 Primary Endpoint

Proportion of subjects reporting good, very good, or excellent on a patient global assessment (PGA) for pain control at the end of treatment

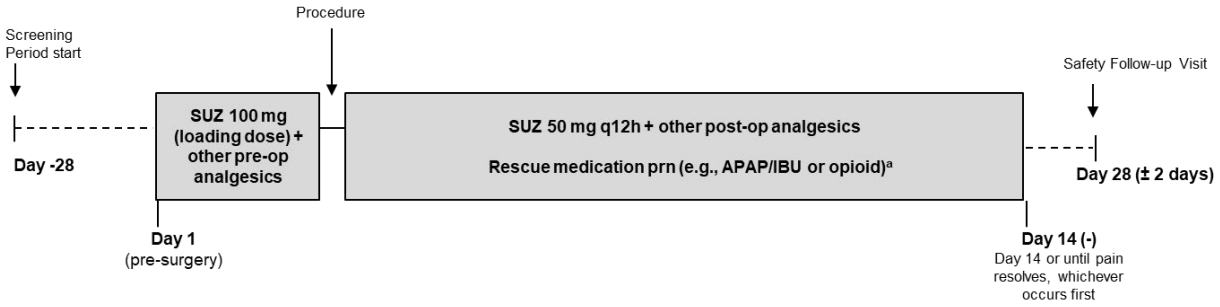
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7 OVERALL DESIGN

This is a Phase 4, open-label, single-arm study evaluating the effectiveness and safety of SUZ as part of MMT for acute pain after aesthetic or reconstructive surgery (**Figure 7-1**).

Figure 7-1 VX24-548-113 Study Design



APAP: acetaminophen; ATC: around the clock; IBU: ibuprofen; NSAID: nonsteroidal anti-inflammatory drug; prn: as needed; post-op: postoperative; pre-op: preoperative; q12h: every 12 hours; SUZ: suzetrigine

Notes: Other preoperative analgesics, if utilized, should be administered at approximately the same time as the loading dose of SUZ. Pre-, intra- and postoperative analgesics will be administered by the subject's physician based on the standard of care for the surgical procedure (e.g., APAP, NSAIDs, dexamethasone, gabapentin [≤600 mg]). Figure is not drawn to scale.

[a] The recommended postoperative standing analgesics (in addition to SUZ) are APAP and IBU (administered together ATC), however, alternative postoperative standing analgesics may be prescribed at the discretion of the subject's physician. If a subject is not taking either APAP or IBU as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be APAP and IBU (administered together prn). If a subject is taking either APAP or IBU (but not both) as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be whichever medication was not included (e.g., if a subject was taking APAP as part of postoperative standing analgesia, IBU would be used as first-tier rescue medication). A subject for whom IBU is contraindicated may participate in the study and take APAP alone. For these subjects, if APAP is already included as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication. For subjects who use APAP and/or IBU as first-tier rescue medication, an orally administered opioid may be used as second-tier rescue medication. If a subject is taking both APAP and IBU as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication.

Approximately 100 subjects will be enrolled to receive SUZ (100 mg first dose, then 50 mg every 12 hours [q12h]). Subjects will receive study drug (SUZ) for 14 days or until their pain resolves, whichever occurs first. Pain is considered to be resolved if a subject decides they no longer need study drug for pain relief and discontinues further dosing. Subjects are encouraged

to have taken at least 6 doses of SUZ postoperatively before deciding to complete treatment due to pain resolution.

On Day 1, subjects will undergo the procedure. The first (loading) dose of SUZ (100 mg) will be administered preoperatively. Postoperatively, subjects will start the maintenance dose of SUZ (50 mg q12h; starting 12 hours after the first dose of SUZ).

All perioperative analgesics (e.g., APAP, NSAIDs, dexamethasone, gabapentin [≤600 mg], nerve block, local anesthetic infiltration) except SUZ will be administered at the discretion of the subject's physician based on standard of care for the surgical procedure (within study restrictions, Section **Error! Reference source not found.** of the CSP).

Preoperative analgesics include any agent (including SUZ) that is administered on Day 1, prior to the subject undergoing the procedure. Intraoperative analgesics include analgesic medications administered by the anesthesiologists through the end of surgery (i.e., incision closed and surgery deemed complete). Postoperative standing analgesics include any agent that is administered on an around-the-clock (ATC) basis (including SUZ) from the end of surgery for a specified duration (e.g., 48 hours) by the physician. A rescue medication is any analgesic that is used as needed postoperatively (in addition to the physician-directed postoperative standing analgesics, including SUZ) if a subject does not experience pain relief that is acceptable to them and requires additional pain medication. Rescue medication may be used at any time postoperatively.

The recommended postoperative standing analgesics (in addition to SUZ) are APAP and IBU (administered together ATC); however, alternative postoperative standing analgesics may be prescribed at the discretion of the subject's physician. If a subject is not taking either APAP or IBU as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be APAP and IBU (administered together prn). If a subject is taking either APAP or IBU (but not both) as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be whichever medication was not included (e.g., if a subject was taking APAP as part of postoperative standing analgesia, IBU would be used as first-tier rescue medication). A subject for whom IBU is contraindicated may participate and take APAP alone. For these subjects, if APAP is already included as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication. For subjects who use APAP and/or IBU as first-tier rescue medication, an orally administered opioid may be used as second-tier rescue medication. If a subject is taking both APAP and IBU as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication.

All subjects should be informed that they are encouraged to wait at least 60 minutes after taking a dose of first-tier rescue medication before use of the opioid rescue.

MMT is considered complete after the end of SUZ treatment (i.e., at latest Day 14). Analgesics used after the end of SUZ treatment (postoperative standing analgesics or prn medications) are not considered MMT or rescue medication.

7.1 Sample Size and Power

Approximately 100 subjects are planned to be enrolled. With a sample size of 100, the half width of the 95% CI for the proportion of subjects reporting good, very good, or excellent in PGA at the end of treatment will be no more than 10%.

7.2 Randomization

This is a single-arm study with no randomization.

7.3 Blinding and Unblinding

This is an open-label study.

8 ANALYSIS SETS

8.1 All Subjects Set

The **All Subjects Set** is defined as all subjects who were enrolled (defined as subject having data in the clinical database). The All Subjects Set will be used for individual subject data listings and disposition summary tables unless otherwise specified.

8.2 Modified Full Analysis Set

The **Modified Full Analysis Set (mFAS)** is defined as all subjects who have received at least 1 dose of study drug, excluding subjects who meet one of the postoperative individual stopping rules before discharge/leaving the medical facility (as defined in Section 9.8 of the CSP). Subjects/sites with major quality issues that can affect effectiveness outcomes may be excluded from the mFAS.[*] The mFAS will be used for effectiveness analyses 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.

8.4 Interim All Subjects Set

The **Interim All Subjects Set** will include subjects in the All Subjects Set who were enrolled at least 14 days before the IA data cutoff date. The Interim All Subjects Set will be used during the IA for individual subject data listings and disposition summary tables, unless otherwise specified.

8.5 Interim Full Analysis Set

The **Interim Full Analysis Set (iFAS)** will include subjects in the mFAS who completed the Day 14 or End of Dosing Visit (or discontinued treatment early) and who received their first dose at least 14 days before the IA data cutoff date. The iFAS will be used during the IA for subject demographics, baseline characteristics, and all effectiveness analyses, unless otherwise specified.

8.6 Interim Safety Set

The **Interim Safety Set (IA Safety Set)** will include subjects in the Safety Set who completed the Day 14 or End of Dosing Visit (or discontinued treatment early) and who received their first

[*] Exclusion will be identified and documented.

dose at least 14 days before the IA data cutoff date. The IA Safety Set will be used during the IA for safety analyses.

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 enrolled subjects 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).

Categorical variables will be summarized using frequencies and percentages.

Baseline value, unless specified otherwise, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug. For ECGs, the baseline value will be defined as the average of the non-missing pretreatment measurements (triplicate; scheduled or unscheduled) before the first dose of study drug.

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 to the Safety Follow-up Visit or to the completion of study participation (as defined in Section 9.1.5 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.

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

Multiplicity: No statistical hypothesis testing will be performed.

9.2 Background Characteristics

9.2.1 Subject Disposition

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

- All Subjects Set/Enrolled

- Modified Full Analysis Set (mFAS)
- Safety Set
- Enrolled but not dosed

The number and percentage of subjects in each of the following disposition categories will be summarized:

- Completed treatment and the reason for completion of treatment
- Prematurely discontinued treatment (including those who discontinued treatment due to postoperative stopping rules before discharge/leaving the medical facility) and the reason for discontinuation from treatment
- Completed study
- Prematurely discontinued the study and the reason for discontinuation from study

A disposition listing of subjects will be provided.

9.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized based on the mFAS.

Demographic data will include the following:

- Age at screening (in years)
- Age at screening category (≥18 to <65, ≥65 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)
- Surgical procedures
- Site

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

- Informed consent
- Inclusion/exclusion criteria violation for enrolled subjects

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 mFAS by MedDRA system organ class (SOC) and preferred term (PT). The corresponding data listing will also be provided.

9.2.4 Prior and Concomitant Medications

Prior and concomitant medications will be summarized based on the mFAS by Preferred Name.

Medications will be coded using the World Health Organization Drug Dictionary and categorized as the following for the purpose 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.

Pre- and intra-operative medication: Medication used pre- or intra-operatively.

Prior medications, concomitant medications, and pre- and intra-operative medications will be summarized separately by the proportion of subjects taking any medication and proportion of subjects taking each medication.

Prior and concomitant non-pharmacological treatments or procedures will also be listed. Imputing missing or partial start/end date and time of medication are described in **Appendix B**.

9.2.5 Study Drug Exposure

Study drug exposure (in days) will be calculated as (last date of dosing – first date of dosing) + 1. This will be summarized overall based on the mFAS, as well as separately for those who completed treatment and for those who discontinued treatment. Study drug exposure will also be summarized in the following categories: ≤72 hours after surgery, >72 hours after surgery to ≤7 days, >7 to ≤10 days, >10 to ≤14 days, and >14 days using numbers and percentages of subjects.

All data collected during dispensation of study drug (e.g., time of administration and number of tablets 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 data lock. IPDs will be identified by the PD review team according to the protocol deviation plan.

IPDs will be summarized descriptively based on the mFAS and presented in an individual data listing.

9.3 Effectiveness Analysis

All effectiveness analyses will be performed based on the mFAS, unless otherwise specified.

9.3.1 Analysis of Primary Endpoint

The primary endpoint is the proportion of subjects reporting good, very good, or excellent on a patient global assessment (PGA) for pain control at the end of treatment. The PGA will be evaluated on a 5-point Likert scale (poor, fair, good, very good, or excellent). The proportion of subjects reporting good, very good, or excellent in PGA at the end of treatment will be presented descriptively based on the mFAS, as well as 95% exact confidence interval using Clopper Pearson method. The proportion of subjects providing each response from the 5-point Likert scale will be also summarized.

The PGA at the end of treatment is defined as either the PGA collected on Day 14 or the PGA associated with the End of Dosing Visit for subjects who complete or discontinue study drug treatment before Day 14. Additional details are provided in **Appendix A**. Missing PGA assessments at the end of treatment will be imputed using the last available PGA assessment. Subjects without any PGA will be removed from this analysis.

[redacted]



9.4 Safety Analysis

All safety analyses will be performed based on the Safety Set.

The following safety and tolerability assessments will be used to evaluate the overall safety profile of SUZ:

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., hematology and serum chemistry)
- Standard 12-lead ECG outcomes
- Vital signs

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 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 in **Appendix D.**

AE summary tables will be presented only for TEAEs, 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, a listing 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 and chemistry results will be summarized per visit. Coagulation results will be summarized at screening only.

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 E**.

Results of 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, >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 ANALYSES

The CSP states that interim analyses may be performed during the study. The analysis plan for interim analysis will follow the final analysis plan as outlined in this SAP as appropriate. General considerations, reporting conventions, and analysis methods specified for the final analysis apply to the IA, unless otherwise specified.

An IA is planned when approximately 63 subjects have completed the Day 14 or End of Dosing visit (or discontinued treatment early) and received their first dose at least 14 days before the data cutoff date.

For the IA purpose, the **treatment-emergent (TE) period** will include the time from the first dose of study drug to Safety Follow-up Visit, the completion of study participation (as defined in Section 9.1.5 of the CSP), or the IA data cutoff date, whichever occurs first.

The iFAS will be used during the IA for subject demographics, baseline characteristics, and all effectiveness analyses, unless otherwise specified (**Section 8.5**). The IA Safety Set will be used during the IA for safety analyses (**Section 8.6**).

11 REFERENCES



12 LIST OF APPENDICES

Appendix A: Analysis Visit Windows for Effectiveness and Safety Assessments

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

Assessment	Visit/Timepoint[1]	Target Study Day	Analysis Visit Window (in study days/timepoints)[2,3]
Effectiveness Assessments			
PGA[4,5]	Day 3 Day 7 End of Treatment	3 7 After treatment completion/discontinuation (last dose)	[1, 4] [5, 10] First assessment after subject's last dose of VX-548
[redacted]			
Safety Assessments			
Vital Signs	Baseline Post-op Day 7 End of Treatment Safety Follow-Up	1 (pre-op) Day of discharge 7 After treatment completion/discontinuation 28	≤1 Pre-dose Nominal Nominal Nominal (Day 14 or EDV) Nominal
Standard 12-lead ECG	Baseline End of Treatment Safety Follow-Up	1 (pre-op) After treatment completion/discontinuation 28	≤1 Pre-dose Nominal (Day 14 or EDV) Nominal
Serum chemistry	Baseline Post-op End of Treatment Safety Follow-Up	Screening Visit Day of discharge After treatment completion/discontinuation 28	≤1 Pre-dose Nominal Nominal (Day 14 or EDV) Nominal
Hematology	Baseline Post-op End of Treatment Safety Follow-Up	Screening Visit Day of discharge After treatment completion/discontinuation 28	≤1 Pre-dose Nominal Nominal (Day 14 or EDV) Nominal

[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, EDV, 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 will be used; or
   ii. For Day 3 and Day 7 PGA,
      i. If there are multiple measurements on the same day, the first measurement will be used.
      ii. If there are multiple measurements within the same distance (in days) from the target day and not the same day, the latest measurement will be used.
   iii. If a subject completes or discontinues treatment early, a PGA assessment may map to multiple analysis visit windows (e.g. Day 7 and End of Treatment).

[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] If no PGA measurement is available within the analysis visit window, the PGA will be imputed with the previous PGA measurement if available.

[5] PGA must be between 0 and 48 hours after subject's last dose of VX-548.

Appendix B: Imputation Rules for Missing Medication Information

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.

In summary, the prior or concomitant categorization of a medication is described below.

Table 12-1-1 Prior and 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	P C
≥ First dose date and ≤ End date of TE period	-	C

P: Prior; C: Concomitant

Imputation rules for missing and/or partial dates of non-pharmacological treatment/procedure will follow the same imputation rule.

[redacted]



Appendix D: 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 E: 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	

Signature Page for: VV-CLIN-106374

