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VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX22-548-107 (Final Analysis)

A Phase 3, Single-arm Study Evaluating the Safety and Effectiveness of VX-548 for Acute Pain

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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 safety and effectiveness endpoints defined in the study protocol of VX22-548-107 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.

5 STUDY OBJECTIVES

5.1 Primary Objective

To evaluate the safety and tolerability of VX-548

5.2 Secondary Objective

To evaluate the effectiveness of VX-548 in treating acute pain

6 STUDY ENDPOINTS

6.1 Primary Endpoint

Safety and tolerability based on treatment-emergent adverse events (TEAEs), laboratory test results, vital signs, and ECGs

6.2 Secondary Endpoint

Subject perception of VX-548 effectiveness in treating pain at the end of treatment as measured by the proportion of subjects reporting good, very good, or excellent on a patient global assessment (PGA)

7 OVERALL DESIGN

This is a Phase 3, single-arm study evaluating the safety and effectiveness of VX-548 in treating acute pain (Figure 7-1 [surgical subjects] and Figure 7-2 [non-surgical subjects]).

Surgical Subjects

On Day 1, subjects will undergo a scheduled ambulatory surgical procedure with pain that is expected to last for at least 72 hours and that is expected to require no more than a short-term (i.e., <24-hour) admission. After surgery completion, a subject will be assigned to treatment 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 (verbal categorical rating scale), and (3) the subject's pain is

≥4 on the NPRS (numeric pain rating scale). If a subject does not meet the VRS and NPRS criteria within the protocol-specified time period for the surgical procedure they underwent (e.g., 4 hours for most procedures), the subject will not be eligible for this study.

Non-surgical Subjects

On Day 1, after completion of screening assessments and confirmation of eligibility, a subject will begin treatment if (1) the subject's pain is moderate or severe on the VRS, and (2) the subject's pain is ≥4 on the NPRS. For a subject to be eligible, their pain must have been ongoing for ≤48 hours at presentation.

All Subjects

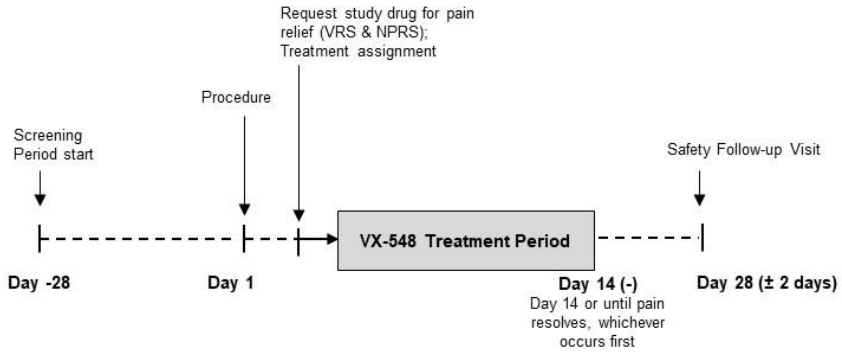
Approximately 250 subjects will receive VX-548 (100 mg first dose, then 50 mg every 12 hours [q12h]). Subjects will continue to receive VX-548 for 14 days or until their pain resolves, whichever occurs first. An acetaminophen/ibuprofen combination may be used as a rescue medication for pain relief as needed (prn), starting any time after the first dose of study drug through Day 14, completion of study drug treatment due to pain resolution, or study drug discontinuation, whichever occurs first. Subjects will be permitted to take acetaminophen 650 mg/ibuprofen 400 mg every 6 hours (q6h) prn, up to a maximum of 2600 mg/1600 mg in any 24-hour period.

The following approach will be used to define pain resolution and completion of study drug treatment:

1. Pain is considered to be resolved and the study drug treatment will be considered completed if
    a. a subject takes no study drug during a 48-hour period (i.e., skipped at least 4 consecutive doses due to pain resolution); and
    b. a subject takes no more than 1 dose of acetaminophen/ibuprofen during each 24-hour period within the 48-hour period (i.e., no more than 2 doses in 48 hours).
2. If a subject stops taking study drug per Criterion 1a but does not meet Criterion 1b, they will be instructed to restart study drug (and prn rescue medication).
3. If a subject stops and restarts study drug (Criterion 2 above) and subsequently believes their pain is resolving and stops study drug a second time, they will be instructed to not restart study drug, regardless of whether the above criteria are met.
4. If a subject stops study drug a second time after the restart of dosing (Criterion 3 above) and then fulfills both Criterion 1a and 1b, the pain is considered resolved and study drug treatment will be considered completed. If the subject fulfills only Criterion 1a but not Criterion 1b after the restart of dosing, the pain is considered not resolved and study drug will be considered discontinued.

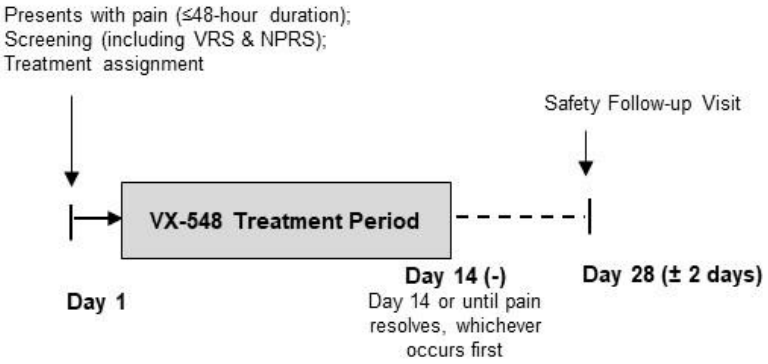
Note: If subject stops study drug due to pain resolution less than 48 hours before the last scheduled dose of study drug (i.e., stops after the second dose on Day 12) and therefore cannot meet Criterion 1a by Day 14, the subject will be considered to have completed study drug dosing as long as they also meet Criterion 1b.

Figure 7-1 VX22-548-107 Study Design (Surgical Subjects)



NPRS: numeric pain rating scale; VRS: verbal categorical rating scale
Notes: After surgery completion, a subject will be assigned to treatment 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 the protocol-specified, procedure-specific time period, the subject will not be eligible for this study. Figure is not drawn to scale.

Figure 7-2 VX22-548-107 Study Design (Non-surgical Subjects)



NPRS: numeric pain rating scale; VRS: verbal categorical rating scale
Notes: After completion of screening assessments and confirmation of eligibility, a subject will be assigned to treatment if (1) the subject's pain is moderate or severe on the VRS, and (2) the subject's pain is ≥4 on the NPRS. Figure is not drawn to scale.

7.1 Sample Size and Power

Approximately 250 subjects are planned to be enrolled. With 250 subjects, there is a 92% probability of observing an AE in at least 1 subject if the true incidence is 1% and a 99% probability of observing an AE in at least 1 subject if the true incidence is 2%.

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.

8.2 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.

8.3 Full Analysis Set

The **Full Analysis Set (FAS)** is defined as all subjects who have received at least 1 dose of study drug. The FAS will be used for effectiveness 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 individual subject data for subjects who have 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).

Categorical variables will be summarized using counts 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 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 to the Safety Follow-up Visit or to the completion of study participation (as defined in Section 9.1.7 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 PGA entries, which are provided by the subject in a dosing diary, are provided in Appendix A. All safety assessments are analyzed according to their nominal visits.

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

Multiplicity: Only descriptive analyses will be performed; 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
- Full Analysis Set (FAS)
- Safety Set
- Enrolled 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 and the reason for completion of 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 of subjects will be provided.

9.2.2 Demographics and Baseline Characteristics

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

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)
- NPRS
- NPRS category (<8, ≥ 8)
- VRS (moderate, severe)
- Surgical/non-surgical status
- Surgery type
- Site

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). 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 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

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. Pre- and intra-operative medications and supplemental analgesic medications for surgical subjects will be included in the summary of prior medications. Rescue medication taken prior to the subject's last dose of VX-548 will be included in the summary of concomitant medications. The proportion of subjects taking any rescue medication will be summarized separately. In addition, for acetaminophen and ibuprofen separately, the mean dose administered per day of VX-548 exposure (calculated for each subject as the total dose / number of days of exposure) will be summarized.

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

9.2.5 Study Drug Exposure and Study Drug Compliance

Study drug exposure (in days) will be calculated as (last date of dosing – first date of dosing) + 1. This will be summarized overall, as well as for those who completed treatment and for those who discontinued treatment. Study drug exposure will also be summarized in categories: ≤3 days, >3 to ≤7 days, and >7 days, using counts and percentages.

Compliance will not be analyzed due to the complex nature of starting and stopping the study drug as explained in Section 9.1 of the CSP.

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 database lock. IPDs will be identified by the PD review team according to the protocol deviation plan.

IPDs will be summarized descriptively and presented in an individual data listing.

9.3 Effectiveness Analysis

The secondary endpoint is the subject perception of VX-548 effectiveness in treating pain at the end of treatment as measured by the proportion of subjects reporting good, very good, or excellent on a patient global assessment (PGA). The PGA of study drug is a single-item assessment of patient perceptions of the method of pain control with the study drug and 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, at the end of treatment will be presented descriptively based on the FAS, as well as the proportion of subjects providing each response. 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. Missing PGA assessments at the end of treatment will be imputed using the previous PGA assessment. Subjects with no previous PGA assessments available will be considered non-responders and will be included in the denominator when calculating the proportions.

9.4 Safety Analysis

The following safety and tolerability assessments will be used to evaluate the overall safety profile of VX-548:

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (hematology, serum chemistry, coagulation, and urinalysis)
- ECG outcomes
- Vital signs
- Columbia-Suicide Severity Rating Scale (C-SSRS)

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

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 C.

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, 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, >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.

9.4.6 Columbia-Suicide Severity Rating Scale

For each event category on the C-SSRS (suicidal ideation, suicidal behavior, suicidal ideation or behavior, self-injurious behavior without suicidal intent), the proportion of subjects with at least one event in the category during the TE Period will be summarized. C-SSRS results for subjects with responses of "Yes" at any visit will also be presented in an individual subject data listing.

9.5 Subgroup Analyses

All summaries of safety, effectiveness, and use of rescue medication will be presented for surgical subjects. These summaries will also be presented for non-surgical subjects if they constitute at least 10% of the total subjects; otherwise, data for non-surgical subjects will be presented in listings only. Due to the underlying differences in the subgroup populations and potentially limited sample sizes in the non-surgical subgroup, these analyses should be interpreted with caution.

Additionally, the proportion of subjects receiving fentanyl citrate, the median dose, and time from last administration of fentanyl citrate to the first dose of study drug among surgical subjects will be summarized in a separate table.

10 SUMMARY OF INTERIM AND IDMC ANALYSES

Interim analyses may be performed during the study. If these occur, the timing and details of the interim analyses will be documented in the SAP prior to its finalization.

11 REFERENCES

Not applicable.

12 LIST OF APPENDICES

Appendix A: Analysis Visit Windows for Effectiveness Assessments

Table 12-1 Analysis Visit Windows for Effectiveness Assessments

Assessment	Visit/Timepoint	Target Study Day	Analysis Visit Window (in study days/timepoints)
PGA	EDV	After treatment completion/discontinuation	First assessment between 0 and 48 hours after subject's last dose of VX-548

Note: If no PGA measurement is available within the EDV visit window, PGA at EDV will be imputed with the previous PGA measurement, if available.

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	