1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX20-445-121 Version 2.0 (Final Analysis)

A Phase 3b Open-label Study Evaluating the Safety of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Cystic Fibrosis Subjects

Authors of SAP: [redacted]

Version: 1.0
Version Date of SAP: 12 December 2022

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

2 TABLE OF CONTENTS

3 MODIFICATIONS

[redacted]

4 INTRODUCTION

Study VX20-445-121 (Study 445-121) is a Phase 3b open-label study evaluating the safety of elexacaftor (ELX, VX-445) in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects with cystic fibrosis (CF) who complete a parent study (VX19-445-117 or VX20-445-126).

This statistical analysis plan (SAP) 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 (Methods) documents the planned statistical analyses of safety endpoints defined in the VX20-445-121 study protocol. It also documents analyses for additional safety variables not specified in the protocol, which will provide supportive information for the scientific understanding of the drug entity.

The Vertex Biometrics Department will perform the statistical analysis of safety data; SAS (Version 9.4 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the clinical database lock. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP.

5 STUDY OBJECTIVES

5.1 Primary Objective

To evaluate the safety and tolerability of ELX/TEZ/IVA in subjects with CF.

6 STUDY ENDPOINTS

6.1 Primary endpoint

Safety and tolerability of treatment with ELX/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry.

7 STUDY DESIGN

7.1 Overall Design

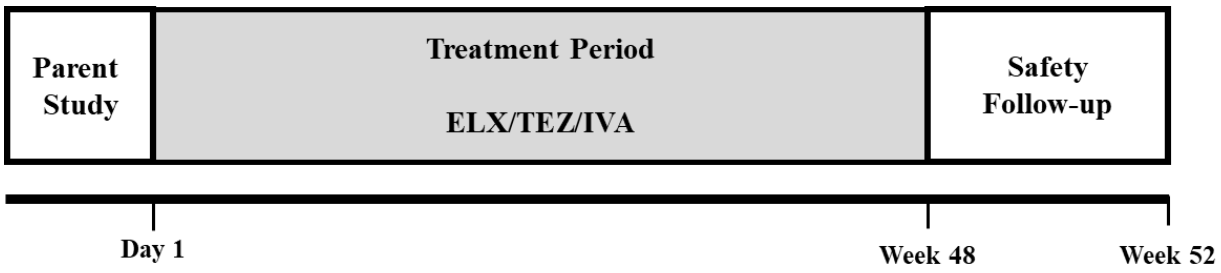
This is a Phase 3b, multicenter, open-label study for subjects who complete a parent study (VX19-445-117 or VX20-445-126) and meet eligibility criteria (Section 8 of the CSP). Subjects will receive a dose of ELX 200 mg once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h). A schematic of the study design is shown in Figure 7-1.

For treatment continuity in regions where ELX/TEZ/IVA is not commercially available, an option to return to this study will be offered to subjects who depart this study to enroll in another qualified Vertex study based on the following:

- Subjects have received open-label ELX/TEZ/IVA during the other study's Run-in Period but have not received study drug in the Treatment Period of the other study, and
- Meet all eligibility criteria for this study (Section 8 of the CSP) at their Returning Visit.

Subjects who resume participation in this study will resume treatment with study drug after completion of a Returning Visit. Resumption of participation in this study following departure to another qualified Vertex study will be permitted only once.

Figure 7-1 VX20-445-121 Study Design



ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor
Note: Figure is not drawn to scale.

7.2 Sample Size and Power

The primary objective of the study is the evaluation of the safety of ELX/TEZ/IVA. This is an open-label extension study that will enroll the subjects from parent studies who meet eligibility criteria in this study.

Up to approximately 160 subjects are expected to enroll in this open-label extension study.

8 ANALYSIS SETS

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

The **Safety Set** is defined as all subjects who have received at least 1 dose of study drug in this study. This analysis set will be used for subject demographics and baseline characteristics and for all safety analyses unless otherwise specified.

9 STATISTICAL ANALYSIS

9.1 General Considerations

The precision standards for reporting safety variables are provided in an internal Biometrics document that specifies the programming rules including the precision for derived variables.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, median, minimum value (min), and maximum value (max).

Categorical variables will be summarized using counts and percentages.

Baseline value, unless otherwise specified, will be the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of ELX/TEZ/IVA in a parent study, as applicable.

Change (absolute change) from baseline will be calculated as Post-baseline value − Baseline value.

Treatment-emergent (TE) Period will include the time period starting from the date of the first dose of study drug of this open-label study to 28 days after the last dose of the study drug, or to the completion date of study participation (as defined in Section 9.1.5 of study protocol), whichever occurs first.

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

1) In scheduled visit windows per specified visit windowing rules
2) In the derivation of baseline and last on-treatment measurements
3) In the derivation of maximum and minimum values during the TE period
4) 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 will not be imputed, unless specified otherwise.

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

9.2 Background Characteristics

9.2.1 Subject Disposition

Subject disposition will be summarized for the All Subjects Set. The number and percentage of subjects in the following categories will be summarized as appropriate:

- All Subjects Set
- Safety Set
- Completed Treatment
- Prematurely discontinued treatment and the reasons for discontinuation
- Completed study
- Prematurely discontinued study and the reasons for discontinuation
- Departed Study VX20-445-121 to participate in another qualified Vertex study
- Departed Study VX20-445-121 to participate in another qualified Vertex study and returned to VX20-445-121

A listing will be provided for subjects who discontinued treatment or who discontinued study with reasons for discontinuation. A separate listing will be provided for subjects who depart from the study.

9.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by descriptive summary statistics for the Safety Set. Demographic data will include the following:

- Age at parent study baseline (in years)
- Sex (female and male)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Collected per Local Regulations and Other)
- Country

Parent study baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

Disease characteristics based on parent study baseline will include the following:

- $ppFEV_1$ at parent study baseline (<30, ≥30 to <40, ≥ 40 to <70, ≥70 to ≤90, and >90)
- $ppFEV_1$ at parent study baseline (continuous)
- Prior use of dornase alfa (Yes, No)
- Prior use of azithromycin (Yes, No)
- Prior use of inhaled antibiotic (Yes, No)
- Prior use of any bronchodilator (Yes, No)
- Prior use of any inhaled bronchodilator (Yes, No)
- Prior use of any inhaled hypertonic saline (Yes, No)
- Prior use of any inhaled corticosteroids (Yes, No)

Prior medication use definition is same as that for the baseline characteristics summary presented in the parent studies.

9.2.3 Medical History

Medical history (referenced to the start of parent study) will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized descriptively by System Organ Class (SOC) and Preferred Term (PT) based on the Safety Set. 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 follows:

- **Prior medication:** any medication that was administered within the 56 days before the first dose of study drug in this open-label study. For subjects who were enrolled in another qualified Vertex study before completing this study and resume participation in this study, any new or changed medication administered after the Departing Visit and prior to the first dose of this study's drug after resuming participation will also be considered as prior medication.
- **Concomitant medication:** medication continued or newly received during the TE Period in this open-label study.
- **Post-treatment medication:** medication continued or newly received after the TE Period in this open-label study.

A given medication may be classified as a prior medication, a concomitant medication, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment.

If a medication has a missing or partially missing start/end date or time and if it cannot be determined whether it was taken before initial dosing, concomitantly during the TE Period, or beyond the TE Period, it will be considered in all 3 categories of prior, concomitant, and post-treatment medication. Details for imputing missing or partial start and/or stop dates of medication are described in Appendix B.

Prior medications and concomitant medications will be summarized descriptively by Preferred Name based on the Safety Set by 1) preferred name (PN); and 2) anatomic class (ATC) level 1, ATC level 2, and PN. Post-treatment medications will be provided separately in an individual subject data listing.

9.2.5 Study Drug Exposure

Study drug exposure will be summarized based on the Safety Set. Duration of study drug exposure (in days) will be calculated as [last dose date – first dose date + 1 day] within the TE period, regardless of any interruption in dosing between the first and the last dose. For subjects who enroll in another qualified Vertex study and resume participation in this study, time spent in the other study will be excluded.

Study drug exposure (in weeks) will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized by interval, using counts and percentages.

9.2.6 Study Drug Compliance

Study drug compliance will be summarized based on the Safety Set, and will be calculated as: $100 \times [1 – (\text{total number of days of study drug interruption in this open-label study}) / (\text{duration of study drug exposure in days in his open-label study})]$. A study drug interruption on a given day is defined as an interruption of any study drug on that day. For subjects who enroll in another qualified Vertex study and resume participation in this study, time spent in the other study will be excluded.

Percentage of study drug compliance will be summarized based on the Safety Set. Percentage of study drug compliance will be summarized descriptively by the number of subjects (n), mean,

SD, median, min, and max. It will also be summarized in categories: <80% and ≥80% using frequency tables.

9.2.7 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. A protocol deviation review team will categorize IPDs according to the Protocol Deviation Plan during the study.

IPDs during this open-label study will be summarized descriptively based on the Safety Set. Additionally, IPDs will be provided in an individual subject data listing.

9.3 Safety Analysis

The primary objective of this study is the evaluation of safety and tolerability of ELX/TEZ/IVA. All safety analyses will be based on the TE Period for subjects in the Safety Set.

The overall long-term safety profile of study drug will be assessed in terms of the following safety and tolerability endpoints:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values
- ECGs
- Vital signs
- Pulse oximetry

Only descriptive analysis of safety will be performed and no statistical testing will be performed.

9.3.1 Adverse Events

AEs will be classified as pretreatment AEs, TEAEs, or post-treatment AEs, defined as follows:

- **Pre-treatment AE**: any AE occurred before the first dose date of study drug in the TE Period. For subjects who were enrolled in another qualified Vertex study before completing this study and resume participation in this study, AEs that started during participation in another qualified Vertex study and were ongoing at the time of Returning Visit will be flagged as pre-treatment AE.
- **TEAE**: any AE that worsened (either in severity or seriousness) or newly developed at or after the first dose date of ELX/TEZ/IVA in the TE Period in this open-label study.
- **Post-treatment AE:** any AE that worsened (either in severity or seriousness) or newly developed after the TE Period.

For AEs with missing or partial start dates, if there is no clear evidence that the AEs started before or after study drug treatment start date in this OLS, then the AEs will be classified as TEAEs.

Details for imputing missing or partial start dates of adverse events are described in Appendix C.

An overview of all TEAEs during TE period will be summarized and include the following categories:

- Number of TEAEs (total number of TEAEs only)
- Subjects with any TEAEs
- Subjects with TEAEs by strongest relationship
- Subjects with TEAEs by maximum severity
- Subjects with TEAEs leading to study drug discontinuation
- Subjects with TEAEs leading to study drug interruption
- Subjects with Grade 3/4/5 TEAEs
- Subjects with related TEAEs
- Subjects with serious TEAEs
- Subjects with related serious TEAEs
- Subjects with TEAE leading to death

The frequency counts and percentages will be presented for the above overview table.

The following summary tables of TEAEs will be presented for overall:

- All TEAEs
- Grade 3/4/5 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 percentages of subjects, subjects with multiple occurrences of the same adverse event 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. Missing severity levels will not be included in the Grade 3/4/5 TEAE summaries; missing relationship will be considered as related and included in the related TEAE and related serious TEAE summaries.

An additional summary table in which the number and percentage of subjects will be presented for TEAEs:

- All TEAEs by PT

All AEs in this OLS, including pre-treatment AEs, TEAEs, and post-treatment AEs, will be presented in an individual subject data listing based on the All Subjects Set. In addition, a listing containing individual subject adverse event data for TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, Grade 3/4/5 TEAEs, SAEs and all deaths will be provided. Listings for SAEs and deaths will include a flag indicating the TEAE status.

9.3.1.1 Adverse Events of Special Interest

For this study, elevated transaminases events and rash events, as determined by MedDRA Preferred Terms in Appendix D, are considered as adverse events of special interest. The corresponding AE data will be summarized in terms of frequency counts.

For treatment-emergent elevated transaminases events and rash events, the following categories will be summarized:

- Subjects with events
- Subjects with events by maximum severity
- Subjects with events leading to treatment discontinuation
- Subjects with events leading to treatment interruption
- Subjects with serious events
- Subjects with study drug related serious events
- Subjects with events leading to death
- Duration of events
- Time-to-onset of first event (with the first dose date of ELX/TEZ/IVA in the open-label study as the reference while calculating time-to-onset)

In addition, for treatment-emergent rash events, the above categories will be summarized for the following subgroups:

- Sex (male, female)
- Female subjects with concomitant hormonal therapy (Yes, No)

9.3.2 Clinical Laboratory Assessments

For the laboratory assessments during TE period, the observed values and change from baseline values of the continuous hematology, coagulation and chemistry results will be summarized in SI units at each visit. Change from baseline in coagulation will be summarized for subjects from parent study 445-117 only.

The number and percentage of subjects meeting at least 1 threshold analysis criterion event during the TE period will be summarized. The threshold analysis criterion shift from baseline will also be summarized for selected laboratory parameters. The threshold analysis criteria are provided in Appendix E.

Results of urinalysis and positive urine/serum pregnancy test will be presented in individual subject data listings only. For positive serum pregnancy listing, subjects with serum HCG which are abnormally high will be selected.

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

9.3.3 Electrocardiogram

For the following ECG interval measurements during the TE period, a summary of observed values and change from baseline values will be provided at each visit (in msec): RR, PR, QT, and QT corrected for HR (QTcF), QRS duration, and HR (beats per minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion event during the TE period will be summarized. The threshold analysis criteria are provided in Appendix E.

9.3.4 Vital Signs

For the vital signs measurements during the TE period, the observed values and change from baseline values will be summarized at each visit. The following vital signs parameters will be summarized: BMI (kg/m^2), weight (kg), systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion event during the TE period will be summarized. The threshold analysis criteria are provided in Appendix E.

9.3.5 Pulse Oximetry

For the percent of oxygen saturation measurements using pulse oximetry during the TE period, a summary of observed values and change from baseline values will be provided at each visit.

The number and percentage of subjects with shift changes from baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the TE period will be summarized.

9.3.6 Physical Examination

No tables/figures/listings will be provided for physical examination data.

9.3.7 Ophthalmology Examination

Ophthalmology examination results will be provided in a data listing.

9.3.8 COVID-19 Impacted Visits

A listing containing subjects' visits impacted due to COVID-19 will be provided.

10 Interim and DMC Analyses

10.1 Interim Analysis

Not applicable.

10.2 DMC analysis

Not applicable.

11 REFERENCES

1. Centers for Disease Control and Prevention. CDC Growth Charts. Available at: http://www.cdc.gov/growthcharts/percentile_data_files.htm.

12 APPENDICES

Appendix A: Analysis Visit Windows for Safety Assessments

Table 12-1 Analysis Visit Windows Safety Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3, 4]
Weight, Height and BMI	Baseline	––	defined in section 9.1
	OL Week 12	85	[1, 127] where Day 1 is post-dose measurement
	OL Week 24	169	(127, 211]
	OL Week 36	253	(211, 295]
	OL Week 48	337	(295, 351]
	OL Safety Follow-up	Not applicable	Use nominal visit
Vital Signs Hematology Serum Chemistry	Baseline	––	defined in section 9.1
	OL Week 12	85	[1, 127] where Day 1 is post-dose measurement
	OL Week 24	169	(127, 211]
	OL Week 36	253	(211, 295]
	OL Week 48	337	(295, 351]
	OL Safety Follow-up	Not applicable	Use nominal visit
Standard 12-lead ECG	Baseline	––	defined in section 9.1
	OL ETT or Departing	Not applicable	Use nominal visit (ETT or Departing Visit)
	OL Safety Follow-up	Not applicable	Use nominal visit
Coagulation[5]	Baseline	––	defined in section 9.1
	OL Week 24	169	[1, 253] where Day 1 is post-dose measurement
	OL Week 48	337	(253, 351]
	OL Safety Follow-up	Not applicable	Use nominal visit

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

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

1. If no numerical measurement is available within a visit window, the measurement will be considered missing for the visit.
2. If there is more than 1 numerical measurement available within a visit window, use the following rules:
   i. The measurement closest to the target day will be used; or
   ii. If there are multiple measurements with the same distance from the target day, the latest measurement will be used. If the latest measurement cannot be determined, then unscheduled visit will be selected.

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

1. Scheduled measurement will be treated as pre-dose observation.
2. Unscheduled measurement will be treated as post-dose observation.

[4] For safety assessments, Safety Follow-up analysis visit will be based on nominal Safety Follow-up visit. If a subject does not have a nominal Safety Follow-up visit but has an ETT visit with study day >351, then the ETT visit will be mapped into Safety Follow-up analysis visit for the corresponding part.

[5] Baseline coagulation applies to subjects from parent study 445-117 only; baseline coagulation will be missing for subjects from parent study 445-126.

Derived Variables for each part:

1. Age (in years) at first dose date and post-baseline visit (for demographics, listing and the calculation of [percent] predicted spirometry variables):

   Obtain the age at informed consent in “yy, mm” format (e.g., 24 years, 6 months) from the Vital Signs (VS) page at the Day 1 Visit and add 0.5 month to convert to days.

   Obtain the informed consent date.

   Then age (in years) at first dose or post-baseline visit = [(first dose date or post-baseline visit date – informed consent date) in days + age at informed consent (in days)]/365.25.

2. Missing first dose date or last dose date

   If the first dose date is missing, use Day 1 visit date.

   If the last dose date of study drug is not available and there is no data to indicate that the subject discontinued treatment, the data cutoff date will be used instead.

   If the subject discontinued treatment and the last dose date is missing or partial date is reported, the last dose date will be imputed based on, in descending order priority, the Early Treatment Termination (ETT) visit date, last visit date before the Safety Follow-up, or the last study drug administration date from EX SDTM domain, as appropriate. The imputation algorithm will ensure the imputed last dose date does not exceed the data cutoff date.

3. Electrocardiogram:

   Baseline is defined in Section 8.1. If multiple ECG measurements are obtained on the same calendar day during the TE period,
   - For summary purpose, the average value will be used as the ECG on that day;
   - For threshold analysis purpose, all ECG values will be used

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

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date (to impute in practical, use the parent study informed consent date).
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last day of the month.
    b. If DAY and Month are both missing, use the last day of the year.
    c. If DAY, Month and year are all missing, assign 'continuing' status to stop date (to impute in practical, use the end of study date).

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

Table 12-2 Prior, Concomitant, and Post 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**	**> End Date of TE Period**
< First dose date of study drug	P	PC	PCA
≥ First dose date and ≤ End date of TE period	-	C	CA
> End date of TE period	-	-	A

P: Prior; C: Concomitant; A: Post

Same imputation rule will be implemented for missing and/or partial dates of non-pharmacological treatment/procedure.

Appendix C: Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined below. If the imputed AE start date is before the informed consent date for the OLS, the AE start date will be imputed using the informed consent date. Ongoing events from the parent study will follow the imputation rule described in the SAP for parent study.

- **If only Day of AE start date is missing:**
    - If the full (or partial) AE end date is NOT before the first dose date of the OLS or AE end date is missing, then
        - if AE start Year and Month are equal to the Year and Month of the first dose date of OLS, then impute the AE start Day as the Day of the first dose date of OLS;
        - else impute the AE start day as 1.
    - else impute the AE start day as 1.
- **If Day and Month of AE start date are missing:**
    - If the full (or partial) AE end date is NOT before the first dose date of the OLS or AE end date is missing, then
        - if AE start Year is equal to the Year of the first dose date of OLS, then impute the AE start Month and Day as the Month and Day of the first dose date of OLS;
        - else impute the AE start Month as January and Day as 1.
    - else impute the AE start Month as January and Day as 1.
- **If Year of AE start date is missing:**

  If the Year of AE start date is missing or AE start date is completely missing then query site.
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then impute the AE start date as the first dose date of the OLS.
    - else impute the AE start date as the informed consent date.

Compare the imputed AE start date with TE period to determine whether the AE is pre-treatment AE, TEAE or post-treatment AE.

Imputation rules for partial AE end date are defined below:

If partial end date, then impute as min (the last day of the month, data cut-off for IA, end of study) if day is missing, or min (Dec, data cut-off for IA, end of study) if month is missing.

Appendix D: Adverse Events of Special Interest

Table 12-7 MedDRA Preferred Terms for Event of Special Interest

Adverse event of special interest	MedDRA preferred terms
Elevated transaminases	Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Transaminases abnormal, Transaminases increased, Liver function test abnormal, Liver function test increased, Hypertransaminasaemia, Hepatic enzyme abnormal, Hepatic enzyme increased
Rash	Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash vesicular, Rash pruritic, Rash follicular, Rash pustular, Nodular rash, Drug eruption, Fixed eruption, Urticaria, Urticaria papular, Urticaria vesiculosa, Urticarial dermatitis, Rash morbilliform, Rash papular, Rash papulosquamous, Rash rubelliform, Rash scarlatiniform , Drug hypersensitivity, Type IV hypersensitivity reaction, Dermatitis, Dermatitis atopic, Epidermolysis, Skin toxicity, Dermatitis allergic, Dermatitis exfoliative, Dermatitis exfoliative generalised, Erythema multiforme, Exfoliative rash, Mucocutaneous rash, Acute generalised exanthematous pustulosis, Cutaneous vasculitis, Urticarial vasculitis, Dermatitis bullous, Drug reaction with eosinophilia and systemic symptoms, Epidermal necrosis, Oculomucocutaneous syndrome, Skin exfoliation, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, Perioral dermatitis, Vasculitic rash, Immune-mediated dermatitis, Penile rash, SJS-TEN overlap, Erythrodermic atopic dermatitis, Scrotal dermatitis, Anal Rash, Generalised bullous fixed drug eruption

Note: The preferred terms listed in the table is based on the MedDRA version applicable at the time of finalization of the SAP. If the MedDRA version is upgraded at the time of the final analysis, the corresponding preferred terms based on the upgraded version will be used in the analysis of adverse events of special interest.

Appendix E: Criteria for Threshold Analysis

Table 12-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

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

Table 12-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
(ALT or AST) and Total Bilirubin	(ALT >3×ULN or AST >3×ULN) and TBILI >2×ULN	FDA DILI Guidance Jul 2009.
GGT	>ULN – ≤ 2.5×ULN >2.5× – ≤ 5.0×ULN >5.0× – ≤ 20.0×ULN >20.0×ULN	CTCAE grade 1-4
Clinical Chemistry (NON-LFT)		
Albumin	<LLN – ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>ULN – ≤ 1.5×ULN >1.5× – ≤ 2×ULN >2× – ≤ 5×ULN >5×ULN	Criteria based upon CTCAE
Creatinine	>ULN – ≤ 1.5×ULN >1.5× – ≤ 3.0×ULN >3.0× – ≤ 6.0×ULN >6.0×ULN	CTCAE grades 1-4
Lipase	>ULN – ≤ 1.5×ULN >1.5× – ≤ 2×ULN >2× – ≤ 5×ULN >5×ULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
Creatine Kinase	>ULN – ≤ 2.5×ULN >2.5× – ≤ 5×ULN >5× – ≤ 10×ULN >10×ULN	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 – ≥ 75.0×10e9 /L <75.0× – ≥ 50.0×10e9 /L <50.0× – ≥ 25.0×10e9 /L <25.0 × 10e9 /L	CTCAE grade 1-4
	Platelet increased >ULN	No CTCAE available

Table 12-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Reticulocytes/Erythrocytes (%)	<LLN >ULN	No CTCAE
Coagulation		
Activated partial thromboplastin time (PTT)	>ULN – ≤ 1.5×ULN >1.5× – ≤ 2.5×ULN >2.5×ULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN – ≤ 1.5×ULN >1.5× – ≤ 2.5×ULN >2.5×ULN	CTCAE grade 1-3

Table 12-4 Threshold Analysis Criteria for Laboratory Tests (for labeling purpose)

Parameter	Threshold Analysis	Comments
Clinical Chemistry (LFT)		
ALT or AST	>3×ULN >5×ULN >8×ULN	For labeling purpose

Table 12-5 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	

Table 12-5 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
QRS	>110 ms	
	>160 ms	
	Increase from baseline ≥20 ms	
	Increase from baseline ≥40 ms	
QTc		To be applied to any kind of QT correction formula.
Borderline	>450 ms and <500ms (Male); >470 ms and <500ms (Female)	
Prolonged*	≥500 ms	
Additional		
	Increase from baseline	
	Increase from baseline >10 ms	
	Increase from baseline >20 ms	
	Increase from baseline >40 ms	
	Increase from baseline >60 ms	

Note: Based on CPMP 1997 guideline.

Table 12-6 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
Pulse Rate	Same as above in ECG category	
SBP increased		809/770 analyses
	>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		Per HV grade 1, 3, plus shift change
	<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	

Table 12-6 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
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	
Weight	Weight gain	CTCAE grade 1-3
	≥5 % increase from baseline	
	≥10 % increase from baseline	
	≥ 20% increase from baseline	
	Weight loss	CTCAE grade 1-3
	≥5 % decrease from baseline	
	≥10 % decrease from baseline	
	≥ 20% decrease from baseline	