VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods) for Final Analysis Part A

Protocol Number VX17-661-116, Version 2.0

A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Tezacaftor in Combination With Ivacaftor in Subjects With Cystic Fibrosis Aged 6 Years and Older, Homozygous or Heterozygous for the *F508del-CFTR* Mutation

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2 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
bpm	beats per minute
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CRF	case report form
ECG	electrocardiogram
eCRF	electronic case report form
[redacted]	[redacted]
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
IDMC	independent data monitoring committee
IVA	ivacaftor
LCI	lung clearance index
LFT	liver function test
LLN	lower limit of normal
max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum value
N	number of subjects
PBO	placebo
[redacted]	[redacted]
PT	preferred term
q12h	every 12 hours
QRS	Q, R, and S-wave define the QRS-complex in an ECG
QT	QT interval: The duration of ventricular depolarization and subsequent repolarization; it is measured from the beginning of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate with Fridericia's correction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
ULN	upper limit of normal
WHODD	World Health Organization Drug Dictionary Enhanced

4 INTRODUCTION

Study VX17-661-116 (Study 116) is a Phase 3, Open-label, rollover study to evaluate the safety and efficacy of long-term treatment with tezacaftor in combination with ivacaftor (TEZ/IVA) in subjects with cystic fibrosis (CF) aged 6 years and older, homozygous or heterozygous for the *F508del-CFTR* mutation.

Study 116 Part A evaluates safety and efficacy of treatment with TEZ/IVA over 96 weeks in subjects aged 6 years and older who were enrolled in parent Study VX15-661-113 Part B (Study 113B) or Study VX16-661-115 (Study 115).

This statistical analysis plan (SAP) is for the final analysis of Study 116 Part A which is based on an approved clinical study protocol (CSP) (Version 2.0, dated 08 November 2019), as well as the most recent approved electronic case report form (eCRF), and the most recent approved eCRF completion guidelines.

This SAP (Methods) documents the statistical analyses and data presentation of the safety and efficacy endpoints during Study 116 Part A for subjects who previously participated in Study 113 Part B or Study 115 and subsequently enrolled in Study 116 Part A.

Due to the outbreak of COVID-19 during Study 116 Part A, to ensure continued safety of subjects who *cannot* travel to the study sites for their visits (for any reason due to COVID 19); specific alternative measures are being implemented to minimize the risk of exposure to COVID 19 (COVID-19 Clinical Study Protocol Addendum for Cystic Fibrosis [Version 2.0, dated 15 May 2020]). This SAP summarizes the additional statistical analyses that are related to these alternative measures.

The Vertex Biometrics Department or designee will perform the statistical analysis described in this document; SAS (Version 9.4 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). This SAP will be finalized and approved prior to the database lock of Study 116 Part A.

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 long-term safety and tolerability of TEZ/IVA in subjects with CF aged 6 years and older, who are homozygous or heterozygous for *F508del* in Part A.

5.2 Secondary Objective

To evaluate the long-term efficacy of TEZ/IVA in subjects with CF aged 6 years and older, who are homozygous or heterozygous for *F508del* in Part A.

6 STUDY ENDPOINTS

6.1 Primary Endpoint

Safety and tolerability of long-term TEZ/IVA treatment in Study 116 Part A will be evaluated based on adverse events (AEs), clinical laboratory values (serum chemistry, hematology, lipids, and vitamins), standard 12-lead ECGs, physical examinations (PEs), vital signs, ophthalmologic examinations, and pulse oximetry.

6.2 Secondary Endpoints

As secondary endpoints, the following efficacy endpoints will be analyzed:

- Absolute change from baseline in lung clearance index$_{2.5}$ (LCI$_{2.5}$; for subjects from Study 115 and the Study 113 Part B LCI Sub study only)
- Absolute change from baseline in sweat chloride
- Absolute change from baseline in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score
- Absolute change from baseline in body mass index (BMI)

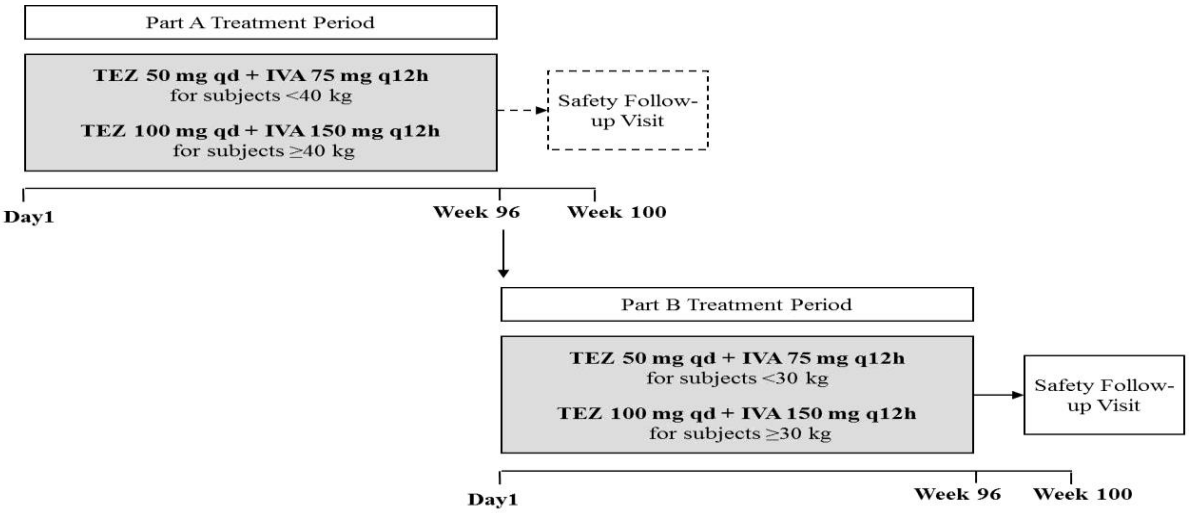
[redacted]

7 STUDY DESIGN

7.1 Overall Design

Study 116 is a Phase 3, multicenter, open-label, 2-part, rollover study in subjects with CF aged 6 years and older, who are homozygous or heterozygous for *F508del* and who completed the Week 24 Visit in Study 113 Part B or the Week 8 Visit in Study 115. A schematic of the study design is shown in Figure 7-1.

Figure 7-1 VX17-661-116 Study Design



Note: Subjects ≥12 years old will receive TEZ 100 mg qd/IVA 150 mg q12h regardless of weight (in Part A and Part B).
IVA: ivacaftor, q12h: every 12 hours, qd: daily, TEZ: tezacaftor

7.2 Sample Size and Power

Study 116 Part A enrolled subjects from Study 113 Part B and Study 115. No formal sample size calculations were performed. Approximately 56 subjects from Study 113 Part B and approximately 65 subjects from Study 115 were potentially eligible for enrollment.

7.3 Randomization

Study 116 Part A is an open-label study with a single treatment arm, and dose is determined by body weight and age. Subjects are not randomized.

7.4 Blinding and Unblinding

Study 116 Part A is an open-label study. Subjects and their parent/caregiver were not informed of their study related LCI, [redacted] or sweat chloride results during the study regardless of whether the subject has prematurely discontinued treatment or not.

8 ANALYSIS SETS

The following analysis sets are defined for Study 116 Part A: All Subjects Set, Safety Set, Full Analysis Set, 113B/116 Full Analysis Set, 115/116 Full Analysis Set, and 113B/116 LCI Full Analysis Set.

Enrolled subjects are those who signed a consent/assent form and had an enrollment date in the CRF for Part A.

All Subjects Set

The **All Subjects Set** will be defined as all subjects who were enrolled in Study 116 Part A or received at least 1 dose of TEZ/IVA in Study 116 Part A. This analysis set will be used for all individual subject data listings and the disposition summary table, unless specified otherwise.

Full Analysis Set (FAS)

The **Full Analysis Set (FAS)** will be defined as all subjects who were enrolled in Study 116 Part A, who received at least 1 dose of TEZ/IVA in Study 116 Part A and have an eligible genotype. The FAS will be used for efficacy analyses, unless otherwise specified.

115/116 Full Analysis Set (FAS), 113B/116 FAS and 113B LCI /116 FAS

The 115/116 FAS will be defined as the subset of FAS who were enrolled in parent Study 115. The 113B/116 FAS will be defined as the subset of FAS who were enrolled in parent Study 113B. The 113B/116 LCI FAS will be defined as the subset of Study 113B subjects who participated in the LCI sub-study in Study 113B.

Safety Set

The **Safety Set** will be defined as all subjects who are in enrolled in study 116 Part A and who received at least 1 dose of TEZ/IVA in Study 116 Part A. The Safety Set will be used for all safety analyses, unless otherwise specified.

9 ANALYSIS PERIOD

The analysis period used for safety and efficacy endpoints is described below.

9.1 Study 116 Analysis Periods

The Safety analysis period is defined as the **treatment emergent (TE) Period**. The safety analysis period begins at the first dose of study drug in Study 116 Part A and ends 28 days after the last dose of study drug in Study 116 Part A, or at the date of Study 116 Part A participation completion, whichever occurs first.

The safety analyses will be performed on the Safety Set over the Safety Analysis Period, unless otherwise specified.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, Physical Exams, ophthalmologic examinations, clinical laboratory values, vital signs, ECG measurements, and pulse oximetry.

Only descriptive summaries will be presented, and no statistical testing is planned.

Completion of study participation in Study 116 Part A is defined as one of the following:

- For subjects who complete Study 116 Part A and do not roll over to Part B: The Safety Follow-up Visit
- For subjects who complete Study 116 Part A and roll over to Part B or transition to Commercial Drug: The Week 96 Visit
- For subjects who prematurely discontinue study drug treatment but do not withdraw consent in Study 116 Part A: the latest of early treatment termination (ETT) Visit, or Safety Follow-up Visit (if applicable)
- For subjects who withdraw consent in Study 116 Part A: date of withdrawal of consent
- For subjects who are lost to follow-up in Study 116 Part A: the date of last contact

The efficacy analysis period begins at the first dose of study drug in Study 116 Part A and ends at the last study visit at which efficacy data are collected in Study 116 Part A as described in the visit window in the Appendix A. The efficacy analysis will be performed on all subjects in the FAS by parent study for the efficacy analysis period, unless specified otherwise.

[redacted]

10 STATISTICAL ANALYSIS

10.1 General Considerations

The Schedule of Assessments is provided in the clinical study protocol (CSP) Table 3-1. The precision standards for reporting safety and efficacy variables are provided in an internal Biometrics document that specifies the programming rules including the precision for derived variables.

All individual subject data for subjects who were enrolled in a parent study and who received at least 1 dose of TEZ/IVA in either parent study or in Study 116 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. Percentages will be presented to 1 decimal place.

Day 1, unless specified otherwise, will be defined as the day of the first dose of TEZ/IVA, in the Study 116 Part A.

Baseline value for safety analysis will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of TEZ/IVA, whether the first dose was taken in the parent study or in Study 116 Part A. For ECGs, the baseline value will be defined as the last non-missing measurement (scheduled or unscheduled) before the first dose of TEZ/IVA or the average of measurements (triplicate) before the first dose of TEZ/IVA, whether the first dose was taken in the parent study or in Study 116 Part A.

Baseline value for efficacy analysis will be defined as the same as baseline of the parent study.

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

Relative change from baseline will be calculated and expressed in percentage as 100% × (Post-baseline value – Baseline value) / Baseline value.

The data from Study 116 will be integrated with data from the parent studies for the purpose of providing robust safety and efficacy analyses.

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

- In scheduled visit windows per specified visit windowing rules.
- In the derivation of baseline measurements.
- In the derivation of maximum/minimum values and maximum/minimum change from baseline values for safety analyses.
- In individual subject data listings as appropriate.

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix A.

Incomplete/Missing data will not be imputed, unless otherwise specified.

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

Multiplicity: No multiplicity adjustment will be performed.

10.2 Background Characteristics

10.2.1 Subject Disposition

A summary table of subjects' disposition will be presented for the All Subjects Set for the following categories:

- All Subjects Set
- Safety Set
- Full Analysis Set

The number and percentage of subjects in each of the following disposition categories will be presented based on the Safety Set:

- Completed study drug treatment in Part A
- Prematurely discontinued the treatment in Part A and the reason for discontinuation
- Completed Safety Follow-up in Part A
- Did not complete Safety Follow-up in Part A and the reason for not completing

A listing will be provided for subjects who discontinued treatment during Study 116 Part A or who discontinued Study 116 Part A, with reasons for discontinuation.

10.2.2 Demographics and Baseline Characteristics

Demographics and treatment baseline characteristics will be summarized based on the FAS, and will be presented by 115/116 FAS, and 113B/116 FAS, and overall. Note: all efficacy analysis will be presented by parent study, hence this may be informative.
Demographic data will include the following:

- Age (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, and Other)
- Geographic region (North America, Europe, and Australia)
- *CFTR* genotype group (*F508del/F508del*; *F508del*/Residual Function)

Baseline characteristics will include the following:

- Weight (kg)
- Weight group (<30 kg, 30-40kg, and ≥40 kg)
- [redacted]
- Height (cm)
- [redacted]
- BMI (kg/m^2)
- [redacted]

Disease characteristics will include the following:

- [redacted]
- [redacted]
- Sweat chloride at treatment baseline

- CFQ-R respiratory domain score at treatment baseline
- $LCI_{2.5}$ at treatment baseline (Study 115 subjects and 113B LCI sub study subjects only)
- 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)
- Infection with Pseudomonas aeruginosa within 2 years prior to parent study screening (Positive, Negative)

Prior medication use refers to medication taken before the first dose date of TEZ/IVA regimen in either the parent study (if the subject received the first dose of TEZ/IVA regimen in the parent study) or Study 116 Part A (if the subject received the first dose of TEZ/IVA regimen in Study 116 Part A).

10.2.3 Medical History

Medical history (referenced to the start of parent study) will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT), and will be summarized based on the FAS and displayed by 115/116 FAS, and 113B/116 FAS, and overall.

10.2.4 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary (WHODD) and categorized as follows:

- **Prior medication:** any medication that started before the first dose date of study drug
- **Concomitant medication:** medication continued or newly received during the TE period. A given medication may be classified as prior, concomitant, or both prior and concomitant. If a medication has a completely missing or partially missing start/stop date and it cannot be determined whether it was taken before the first dose date or concomitantly, it will be classified as prior and concomitant.
- **Post-treatment medication:** medication continued or newly received after the TE period.

Prior medications and concomitant medications will be summarized descriptively by: 1) preferred name (PN); and 2) anatomic class (ATC) level 1, ATC level 2, and PN, based on the 116A FAS and will be presented by 115/116 FAS, and 113B/116 FAS, and overall. Details for imputing missing or partial start and/or stop dates of medication are described in Appendix D.

10.2.5 Study Drug Exposure

Duration of study drug exposure (in days) will be calculated as: last dose date – first dose date + 1 day, regardless of study drug interruption. The first and last dose dates of Study 116 Part A will be used for the calculation.

Study drug exposure will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max based on the 116A Safety Set. It will also be summarized into the following categories: >0 to ≤12 weeks, >12 to ≤24 weeks, >24 to ≤36 weeks, >36 to ≤48 weeks, >48 to ≤60 weeks, >60 to ≤72 weeks, >72 to ≤84 weeks, >84 to ≤96 weeks, >96 weeks, using counts and percentages.

Additionally, the total study drug exposure, defined as the sum of the study drug exposure across all subjects (in patient-years), will be provided.

Exposure summaries will be based on the Safety Set.

10.2.6 Study Drug Compliance

The study drug compliance will be calculated based on the study exposure (in days) as well as based on the number of tablets taken; summary of both calculations will be provided.

Study drug compliance based on study drug exposure will be calculated as: 100 × [1 − (total number of days of any study drug interruption) / (duration of study drug exposure in days)].

Study drug compliance based on the number of tablets taken will be calculated as: 100 x [(total number of tablets dispensed) – (total number of tablets returned)]/(total number of tablets planned to be taken per day x duration of study drug exposure in days). The maximum percentage of tablets taken will be 100%.

Both Study drug compliance variables will be summarized descriptively by the n, mean, SD, median, minimum, and maximum. They will also be summarized in categories: <80% and ≥80% using frequency tables.

Study drug compliance summaries will be based on the FAS, and will be presented by 115-116 FAS, and 113B-116 FAS, and overall.

10.2.7 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. IPD rules will be developed and finalized before the data lock for Part A.

Protocol deviations that should be considered as potential IPDs include, but are not limited to:

- Subject was enrolled in the study despite not satisfying one or more inclusion/exclusion criterion
- Subject was less than 80% compliant with study drug for non-safety reasons
- Subject received prohibited concomitant medications

- Subject received the wrong treatment or incorrect doses
- Subject remained in the study despite meeting withdrawal criteria

The occurrence of any of these events should be considered as a potential IPD, but the team should categorize such an event as an IPD only if it has the potential to affect the completeness, accuracy, or reliability of the study data or the subject's rights, safety, or well-being.

An individual subject data listing and a summary table of IPDs based on the FAS will also be provided.

10.3 Safety Analysis

The primary objective of Study 116 Part A is to evaluate the long-term safety and tolerability of TEZ/IVA. The overall 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
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry
- Ophthalmologic examination

Analysis of AEs will be based on events that occur during the TE period of the Part A, for all subjects in the Safety Set. Pooled AE data from Study 113 Part B and Study 115 (only those who received TEZ/IVA) will be displayed side-by-side with AE data from Study 116 Part A. When displayed side-by-side with parent study results, exposure-adjusted rates will be provided.

Other safety analyses will be based on data from the TE period for all subjects in the Safety Set; and will be presented overall. The Safety Set will be used for all listings unless otherwise specified.

Baseline value will be used to calculate change from baseline for continuous safety endpoints.

Only descriptive summaries will be presented, and no statistical testing is planned.

10.3.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment adverse events (AEs), TEAEs, or post-treatment AEs, defined as follows:

- **Pretreatment AE** any AE that started before the first dose of study drug.
- **TEAE:** any AE that worsened (either in severity or seriousness) or that was newly developed during the TE period.

- **Post-treatment AE:** any AE that worsened (either in severity or seriousness) or that was newly developed after the TE period.

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

Details for imputing missing or partial AE start/end dates are defined in Appendix E.

10.3.1.1 Overview of TEAEs

An overview table of TEAEs will be provided with the following categories:

- Number of TEAEs (total number of TEAEs)
- Subjects with any TEAEs
- Subjects with TEAEs by strongest relationship
- Subjects with TEAEs by maximum severity
- Subjects with related TEAEs
- Subjects with Grade 3/4 TEAEs
- Subjects with serious TEAEs
- Subjects with related serious TEAEs (possibly related, related or missing)
- Subjects with TEAEs leading to treatment discontinuation
- Subjects with TEAEs leading to treatment interruption
- Subjects with TEAEs leading to death

The frequency counts and percentages will be presented for the above overview table. Exposure adjusted event rates may also be provided.

In addition, listings containing individual subject adverse event data for TEAEs leading to treatment discontinuation, treatment interruptions, SAEs and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.

10.3.1.2 TEAEs by SOC and PT

The following summary tables of TEAEs will be provided:

- All TEAEs
- Related TEAEs
- Grade 3/4 TEAEs
- Serious TEAEs
- Related Serious TEAEs (possibly related, related or missing)
- TEAEs by strongest relationship
- TEAEs by maximum severity

- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- 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). For selected summary tables, the exposure adjusted event rate may also be provided.

When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once; only the maximum severity level will be presented in the severity summaries and the strongest relationship level will be presented in the relationship summaries. While summarizing the number of events for the exposure adjusted even rate, all occurrences will be counted.

10.3.1.3 TEAEs and SAEs by PT

The number and percentage of subjects with TEAEs and SAEs will be summarized by PT. Exposure adjusted event rates may also be provided. When summarizing the number and percentage of subjects with an event, multiple occurrences of the same adverse event or a continuing adverse event for the same subject will be counted once. While summarizing the number of events for the exposure adjusted event rate, all occurrences will be counted.

10.3.1.4 TEAEs of Special Interest

For treatment-emergent elevated transaminase events, respiratory symptoms, and respiratory events (PT lists are provided in

Appendix H), the following categories will be summarized in terms of frequency counts:

- 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 related serious events
- Subjects with events leading to death
- Duration of events
- Time-to-onset of first event

10.3.2 Clinical Laboratory Values

For laboratory measurements, the raw values and change from treatment baseline values of the continuous hematology, chemistry, vitamin, and lipids results will be summarized in SI units at each scheduled time point in the TE period based on the Safety Set.

The number and percentage of subjects with laboratory measurements meeting threshold criteria during the TE period will be summarized based on the Safety Set for selected laboratory measurements.

The threshold criterion shift from treatment baseline during the TE period will also be summarized for selected LFT laboratory parameters. The threshold criteria are provided in Appendix G.

A listing of subjects with elevated LFT results during the TE period will be presented based on any of the following: AST >3 × ULN, ALT >3 × ULN, GGT >3 × ULN, ALP >3 × ULN, or total bilirubin >2 × ULN. For each subject in the listing, LFT assessments at all the time points will be included (scheduled and unscheduled).
In addition, a listing containing individual subject hematology and chemistry values outside the normal reference ranges will be provided. This listing will include data from both scheduled and unscheduled visits.
Only central lab results will be used for the tables. Local lab results will be included in the listings.

10.3.3 Electrocardiogram

A summary of raw values and change from treatment baseline values will be provided based on the Safety Set at each scheduled time point in the TE period for the following standard 12-lead ECG measurements: RR (msec), HR (beats per minute [bpm]), PR (msec), QRS duration (msec), QT (msec), and QT corrected for HR intervals (QTcF [msec]).

A listing of ECG assessments of subjects with at least 1 abnormal finding will be provided.

The number and percentage of subjects with at least 1 ECG event meeting the threshold criteria during the TE period will be summarized based on the Safety Set in the TE period. The threshold value criteria are provided in Appendix G.

10.3.4 Vital Signs

For vital signs measurements, the raw values and change from treatment baseline values will be summarized based on the Safety Set at each scheduled time point during the TE period for the following measurements: systolic and diastolic blood pressure (mm Hg), body temperature (°C), HR (bpm), and respiration rate (breaths per minute).

The number and percentage of subjects meeting threshold criteria during the TE period will be summarized by vital signs parameters based on the Safety Set. The threshold value criteria are provided in Appendix G.

10.3.5 Pulse Oximetry

For percent of oxygen saturation by pulse oximetry, a summary of raw values and change from treatment baseline values will be provided at each scheduled time point during the TE period based on the Safety Set.

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

The reference range for normal oxygen saturation is specified as >95%, and <=95% for low oxygen saturation.

10.3.6 Ophthalmologic Examination

Ophthalmologic examination abnormal findings will be presented as a subject data listing.

10.4 Efficacy Analysis

All efficacy analyses described in this section will be performed by parent study based on the FAS (115/116 FAS and 113B/116 FAS) unless specified otherwise. LCI analysis will be based on the 115/116 FAS and the 113B/116 LCI FAS.
The analysis will include all available measurements during the efficacy analysis period.

10.4.1 Analysis of Primary Efficacy Variables

Not applicable

10.4.2 Analysis of Secondary Efficacy Variables

Methods of efficacy analyses will be similar for those used in the parent studies. Each of the secondary endpoints ($LCI_{2.5}$, sweat chloride, BMI, and CFQ-R) will be analyzed using a Mixed Model Repeated Measures (MMRM) model, with absolute change from baseline during the efficacy analysis period as the dependent variable.

Note: For study 113B the change from baseline in $LCI_{2.5}$, will be provided as descriptive summary statistics only.

The model will include the absolute change from baseline as the dependent variable; visit as a fixed effect; and subject as a random effect, and baseline value as a covariate. For

consistency with the models in the parent studies, models for subjects from Study 115 will also include mutation group (F/F vs. F/RF) and baseline LCI2.5 as a fixed effect.

In the model, visit will be treated as a class variable, assuming an unstructured covariance matrix to model the within-subject variability. This model imposes no assumptions on the correlational structure and is considered robust. Denominator degrees of freedom for the *F* test for fixed effects will be estimated using the Kenward-Roger approximation. If there is a convergence problem due to the use of an unstructured covariance matrix, a compound symmetry covariance structure will be used to model the within-subject errors.

With a mixed-effects model based on a restricted maximum likelihood estimation used for the analysis and assuming that, conditional on fixed and random effects, data are missing at random, no imputation of missing data will be performed.

Note: Missing data due to COVID-19 outbreak will be considered as missing at random.

Since the underlying assumption of the MMRM method is that data are missing at random, for the secondary endpoints no further analysis will be performed to investigate the impact of the COVID-19 outbreak.

10.4.2.1 Change from Baseline in Lung Clearance Index $LCI_{2.5}$

The absolute change from baseline in $LCI_{2.5}$ at Day 15, Weeks 4, 24, 48, 72 and 96 will be analyzed using a MMRM as specified above.

The analysis will be performed using a restricted maximum likelihood (REML)-based mixed-effect model for repeated measures (MMRM) for the subjects in the 115/116 FAS only.

For 115/116 FAS , the model will include absolute change from baseline in $LCI_{2.5}$ measurements at Day 15, Weeks 4, 24, 48, 72 and 96 as the dependent variable, and visit (as a class variable), mutation group (F/F and F/RF) as a fixed effects, and baseline $LCI_{2.5}$ (continuous) value as covariate, and subject as a random effect.

For subjects from Study 115, only those who were randomized to TEZ/IVA treatment group will be included in the MMRM model.

For each visit, the LS mean, standard error (SE), and associated 95% CI, will be provided. The LS mean and associated 95% CI at each visit will also be plotted.

The raw values and change from the baseline values of $LCI_{2.5}$ will be summarized for subjects in the 113B/116 LCI FAS at Week 24, 48, 72, 96, for subjects in the 115/116 FAS who were randomized to TEZ/IVA (in Study 115), and for the 115/116 FAS overall at Day 15, Weeks 4, 24, 48, 72 and 96.

10.4.2.2 Absolute Change from Baseline in Sweat Chloride

The absolute change from baseline in sweat chloride at Weeks 24, 48 and 96 will be analyzed using a MMRM as specified above.

The analysis will be performed using a restricted maximum likelihood (REML)-based mixed-effect model for repeated measures (MMRM) for the subjects in the 115/116 FAS and the 113B/116 FAS separately.

For 115/116 FAS , the model will include absolute change from baseline in sweat chloride measurements at Weeks 24, 48 and 96 as the dependent variable, and visit (as a class variable), mutation group (F/F and F/RF) as a fixed effects, and baseline sweat chloride (continuous) value and baseline LCI2.5 as covariates, and subject as a random effect.

For 113B/116 FAS, the model will include absolute change from baseline in sweat chloride measurements at Weeks 24, 48 and 96 as the dependent variable, and visit (as a class variable) as a fixed effect, baseline sweat chloride (continuous) value as covariate, and subject as a random effect.

For subjects from Study 115, only those who were randomized to TEZ/IVA treatment group will be included in the MMRM model.

For each visit, the LS mean, standard error (SE), and associated 95% CI, will be provided. The LS mean and associated 95% CI at each visit will also be plotted.

Additionally, the raw values and change from baseline values of sweat chloride measurements will be summarized for subjects in the 113B/116 FAS , for subjects in the 115/116 FAS who were randomized to TEZ/IVA (in Study 115), and for the 115/116 FAS overall at weeks 24, 48 and 96.

10.4.2.3 Absolute change in the CFQ-R respiratory domain score from baseline

The absolute change from baseline in CFQ-R at Day 15, Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96 will be analyzed using a MMRM as specified above.

The analysis will be performed using a restricted maximum likelihood (REML)-based mixed-effect model for repeated measures (MMRM) for the subjects in the 115/116 FAS and the 113B/116 FAS separately.

For 115/116 FAS, the model will include absolute change from baseline in CFQ-R respiratory score at Day 15, Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96 as the dependent variable, and visit (as a class variable), mutation group (F/F and F/RF) as a fixed effects, and baseline CFQ-R respiratory score (continuous) value and baseline LCI2.5 as covariates, and subject as a random effect.

For 113B/116 FAS, the model will include absolute change from baseline in CFQ-R respiratory score at weeks 12, 24, 36, 48, 60, 72, 84 and 96 as the dependent variable, and visit (as a class variable) as a fixed effect, baseline CFQ-R respiratory score (continuous) value as covariate, and subject as a random effect.

For subjects from Study 115, only those who were randomized to TEZ/IVA treatment group will be included in the MMRM model.

For each visit, the LS mean, standard error (SE), and associated 95% CI, will be provided. The LS mean and associated 95% CI at each visit will also be plotted.

Additionally, the raw values and change from baseline values of CFQ-R measurements will be summarized for subjects in the 113B/116 FAS , for subjects in the 115/116 FAS who were randomized to TEZ/IVA (in Study 115), and for the 115/116 FAS overall at each scheduled time point in Study 116 Part A.

Note: due to COVID-19 outbreak some of the CFQ-R assessments were completed at home, therefore the analysis for the CFQ-R will be performed with and without home assessments included. If the analysis with at-home assessment included is showing inconsistency with the analysis of the in-clinic data only, the in-clinic CFQ-R assessments will be considered as the main analysis.

10.4.2.4 Absolute change from baseline in body mass index (BMI)

The absolute change from baseline in BMI at Day 15, Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96 will be analyzed using a MMRM as specified above.

The analysis will be performed using a restricted maximum likelihood (REML)-based mixed-effect model for repeated measures (MMRM) for the subjects in the 115/116 FAS and the 113B/116 FAS separately.

For 115/116 FAS, the model will include absolute change from baseline in BMI at Day 15, Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96 as the dependent variable, and visit (as a class variable), mutation group (F/F and F/RF) as a fixed effects, and baseline BMI (continuous) value and baseline LCI2.5 as covariates, and subject as a random effect.

For 113B/116 FAS, the model will include absolute change from baseline in BMI at Weeks 12, 24,36, 48, 60, 72,84 and 96 as the dependent variable, and visit (as a class variable) as a fixed effect, baseline BMI (continuous) value as covariate, and subject as a random effect.

For subjects from Study 115, only those who were randomized to TEZ/IVA treatment group will be included in the MMRM model.

For each visit, the LS mean, standard error (SE), and associated 95% CI, will be provided. The LS mean and associated 95% CI at each visit will also be plotted.

Additionally, the raw values and change from baseline values of BMI measurements will be summarized for subjects in the 113B/116 FAS , for subjects in the 115/116 FAS who were randomized to TEZ/IVA (in Study 115), and for the 115/116 FAS overall at each scheduled time point in Study 116 Part A.

[redacted]

12 APPENDICES

▪ Appendix A: Analysis Visit Window Mapping Rules

Table 12-1 Visit Window Mapping Rules for Safety and Efficacy Measurements

Assessments	Parent Study	Study 116 Visit	Target Study Day	Visit Window (in study days)
Safety Assessment				
• Vital Signs • Pulse Oximetry	Study 113 Part B	Baseline	--	Defined in Section 10.1
		116A Week 12	85	[1*, 127]
		116A Week 24	169	(127, 211]
		116A Week 36	253	(211, 295]
		116A Week 48	337	(295, 379]
		116A Week 60	421	(379, 463]
		116A Week 72	505	(463, 547]
		116A Week 84	589	(547, 631]
		116A on Week 96	673	(631, 687]
		116A Safety Follow-up	N/A	Nominal
	Study 115	Baseline	--	Defined in Section 10.1
		116A Day 15	15	[1*, 22]
		116A Week 4	29	(22, 57]
		116A Week 12	85	(57, 127]
		116A Week 24	169	(127, 211]
		116A Week 36	253	(211, 295]
		116A Week 48	337	(295, 379]
		116A Week 60	421	(379, 463]
		116A Week 72	505	(463, 547]
		116A Week 84	589	(547, 631]
		116A Week 96	673	(631, 687]
		116A Safety Follow-up	N/A	Nominal
• Hematology • Serum Chemistry	Study 113 Part B	Baseline	--	Defined in Section 10.1
		116A Week 12	85	[1*, 127]
		116A Week 24	169	(127, 211]
		116A Week 36	253	(211, 295]
		116A Week 48	337	(295, 379]
		116A Week 60	421	(379, 463]
		116A Week 72	505	(463, 547]
		116A Week 84	589	(547, 631]
		116A Week 96	673	(631, 687]
		116A Safety Follow-up	N/A	Nominal
	Study 115	Baseline	--	Defined in Section 10.1
		116A Day 15	15	[1*, 50]
		116A Week 12	85	(50, 127]
		116A Week 24	169	(127, 211]
		116A Week 36	253	(211, 295]

		116A Week 48	337	(295, 379]
		116A Week 60	421	(379, 463]
		116A Week 72	505	(463, 547]
		116A Week 84	589	(547, 631]
		116A Week 96	673	(631, 687]
		116A Safety Follow-up	N/A	Nominal
• ECG • Lipid Panel • Vitamin Levels	Study 113 Part B and Study 115	Baseline	--	Defined in Section 10.1
		116 Week 24	169	[1*, 253]
		116 Week 48	337	(253, 421]
		116 Week 72	505	(421, 589]
		116 Week 96	673	(589, 687]
		116A Safety Follow-up	N/A	Nominal
Efficacy Assessment				
	Study 113 Part B	Baseline	--	Defined in Section 10.1
		116A Week 24	169	[1*, 253]
		116A Week 48	337	(253, 421]
		116A Week 72	505	(421, 589]
		116A Week 96	673	(589, 687]
[redacted] • LCI	Study 115	Baseline	--	Defined in Section 10.1
		116A Day 15	15	[1*, 22]
		116A Week 4	29	(22, 99]
		116A Week 24	169	(99, 253]
		116A Week 48	337	(253, 421]
		116A Week 72	505	(421, 589]
		116A Week 96	673	(589, 687]
• Sweat chloride	Study 113 Part B and Study 115	Baseline	--	Defined in Section 10.1
		116A Week 24	169	[1*, 253]
		116A Week 48	337	(253, 505]
		116A Week 96	673	(505, 687]
• CFQ-R • Weight, height, BMI [redacted]	Study 113 Part B	Baseline	--	Defined in Section 10.1
		116A Week 12	85	[1*, 127]
		116A Week 24	169	(127, 211]
		116A Week 36	253	(211, 295]
		116A Week 48	337	(295, 379]
		116A Week 60	421	(379, 463]
		116A Week 72	505	(463, 547]
		116A Week 84	589	(547, 631]
		116A Week 96	673	(631, 687]
	Study 115	Baseline	--	Defined in Section 10.1
		116A Day 15	15	[1*, 22]
		116A Week 4	29	(22, 57]
		116A Week 12	85	(57, 127]
		116A Week 24	169	(127, 211]
		116A Week 36	253	(211, 295]
		116A Week 48	337	(295, 379]
		116A Week 60	421	(379, 463]

		116A Week 72	505	(463, 547]
		116A Week 84	589	(547, 631]
		116A Week 96	673	(631, 687]

[redacted]

* Only include Day 1 post-dose measurements.

+ Weight will also be used in the threshold analysis in which the treatment baseline will be used to calculate the change; [redacted].

Note:

1. Visit name for analysis purpose is used to report data in tables and figures.
2. The analysis visit windows will be applied for both scheduled and unscheduled visits.
3. If no measurement is available within a visit window, the assessment will be considered missing for the visit.
4. Assessments at early treatment termination (ETT) visit will follow the windowing rules for regular visits up to 116A Week 96 if the ETT visit has a study day ≤ 687; otherwise, the ETT visit will be mapped into 116A Safety Follow-up (SFU) visit, if the subject doesn't have a nominal SFU visit.
5. If there is more than one measurement available within the same visit window for safety parameters, then
   - The record closest to the target day will be used.
   - If there are multiple records within the same distance from the target day, the latest record will be used.
   - SFU visit will not be windowed; instead, it will be used according to the nominal visit in relevant analyses.
6. If there is more than one measurement available within the same visit window for efficacy parameters, the record at the scheduled visit will be used. Otherwise,
   - The record closest to the target day will be used.
   - If there are multiple records within the same distance from the target day, the latest record will be used.
   - SFU visit will not be windowed; instead, it will remain as SFU.
7. [redacted] weight, height, and BMI assessments will be used for both efficacy and safety purposes. Their measurements will follow the visit windowing rules for efficacy parameters.

▪ Appendix B: Standards for Safety Variable Display in TFLs

Continuous Variables

The precision for continuous variables has been specified in the Vertex Standard Programming Rules document (Version 1.0, December 2015):

[redacted]

Categorical Variables: Percentages will be presented to 1 decimal place.

▪ Appendix D: 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 (in practical, use January 01, 2000 to impute).
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 (in practical, use December 31, 2050 to impute).

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

A: Post; C: Concomitant; P: Prior

▪ Appendix E: Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined below:

If only Day of AE start date is missing:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then:
  - If the AE start year and month are the same as that for the first dose date, then impute the AE start day as the day of 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 TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

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 or AE end date is missing, then:
  - If the AE start year is the same as that for the first dose date, then impute the AE start month and day as the month and day of first dose date;
  - Otherwise, impute the AE start month as January and day as 1.
- Otherwise, impute the AE start month as January and day as 1.

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

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 site with no imputation. Also 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 TEAE.

▪ Appendix G: Criteria for Threshold Analysis

Table 12-3 Threshold Analysis Criteria for Clinical Chemistry and Hematology

Parameter	Threshold Criteria	Comments
LFT		
ALT	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN >5 – ≤ 8 xULN >8 – ≤ 20.0 xULN >20.0 x ULN	Per FDA DILI Guidance Jul 2009 and CTCAE
AST	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN >5 – ≤ 8 xULN >8 – ≤ 20.0 xULN >20.0 x ULN	FDA DILI Guidance and CTCAE
ALT or AST	(ALT>ULN and ALT ≤ 3 xULN) or (AST>ULN and AST≤ 3 xULN) (ALT>3 xULN and ALT ≤ 5 xULN) or (AST>3xULN and AST≤ 5 xULN) (ALT>5 xULN and ALT ≤ 8 xULN) or (AST>5xULN and AST≤ 8 xULN) (ALT>8 xULN and ALT ≤ 20 xULN) or (AST>8xULN and AST≤ 20 xULN) ALT>20 xULN or AST> 20 xULN	FDA DILI Guidance
Alkaline Phosphatase	>ULN - ≤ 1.5xULN >1.5 – ≤ 2.5 xULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	FDA DILI Guidance and CTCAE
Total Bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	FDA DILI Guidance and CTCAE
Direct Bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	Same Criteria as Total Bilirubin No CTCAE Not in DILI Guidance
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
GGT	>ULN - ≤ 2.5 x ULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	CTCAE grade 1-4

Non-LFT Chemistry		
CPK	>ULN - ≤ 2.5 x ULN >2.5 - ≤ 5 x ULN >5 - ≤ 10x ULN >10 x ULN	CTCAE grades 1-4
Creatinine	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	CTCAE grades 1-4
Blood Urea Nitrogen	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	Same criteria as creatinine No CTCAE
Sodium	Hyponatremia <LLN - ≥130 mmol/L <130 – ≥120 mmol/L <120 mmol/L	CTCAE grade 1, 3, 4 (No CTCAE grade 2)
	Hypernatremia >ULN - ≤ 150 mmol/L >150 mmol/L- ≤155 mmol/L >155 mmol/L - ≤ 160 mmol/L >160 mmol/L	CTCAE grade 1-4
Potassium	Hypokalemia <LLN – ≥ 3.0 mmol/L <3.0 – ≥ 2.5 mmol/L <2.5 mmol/L	CTCAE grade 1&2, 3, 4 (Grade 1 and 2 are the same)
	Hyperkalemia >ULN – ≤ 5.5 mmol/L >5.5 – ≤ 6.0 mmol/L >6.0 – ≤ 7.0 mmol/L >7.0 mmol/L	CTCAE grade 1-4
Glucose	Hypoglycemia <3.0 – ≥ 2.2 mmol/L <2.2 - ≥ 1.7 mmol/L <1.7 mmol/L	CTCAE grade 1-4
	Hyperglycemia >ULN - ≤ 8.9 mmol/L >8.9 – ≤ 13.9 mmol/L >13.9 – ≤ 27.8 mmol/L >27.8 mmol/L	CTCAE grade 1-4
Albumin	<35 - ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4
Lipase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4

Calcium	Hypercalcemia >ULN - ≤ 2.9 mmol/L >2.9 – ≤ 3.1 mmol/L >3.1 – ≤ 3.4 mmol/L >3.4 mmol/L	CTCAE grade 1-4
	Hypocalcemia <LLN - ≥ 2.0 mmol/L <2.0 – ≥1.75 mmol/L <1.75 – ≥ 1.5 mmol/L <1.5 mmol/L	CTCAE grade 1-4
Magnesium	Hypermagnesemia >ULN - ≤ 1.23 mmol/L >1.23 – ≤ 3.30 mmol/L >3.30 mmol/L	CTCAE grade 1, 3, 4 No CTCAE grade 2
	Hypomagnesemia <LLN - ≥ 0.5 mmol/L <0.5 – ≥ 0.4 mmol/L <0.4 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
Inorganic phosphate	Hypophosphatemia <0.74 – ≥ 0.6 mmol/L <0.6 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
Lipid Panel		
Total Cholesterol	>ULN – ≤ 7.75 mmol/L >7.75 – ≤ 10.34 mmol/L >10.34 – ≤ 12.92 mmol/L >12.92 mmol/L	CTCAE grade 1-4
Triglycerides	>1.71 – ≤ 3.42 mmol/L >3.42 – ≤ 5.7 mmol/L >5.7 – ≤ 11.4 mmol/L >11.4 mmol/L	CTCAE grade 1-4
Hematology		
WBC	WBC decreased <LLN - ≥ 3.0 x 10e9 /L <3.0 – ≥ 2.0 x 10e9 /L <2.0 – ≥ 1.0 x 10e9 /L <1.0 x 10e9 /L	CTCAE grade 1-4
	Leukocytosis >100 x 10e9 /L	CTCAE grade 3 (only Grade available)
Lymphocytes	Lymphocyte decreased <LLN - ≥ 0.8 x10e9 /L <0.8 – ≥ 0.5 x10e9 /L <0.5 – ≥ 0.2 x10e9 /L <0.2 x10e9 /L	CTCAE grade 1-4
	Lymphocyte increased >4 – ≤ 20 x10e9/L >20 x10e9/L	CTCAE grade 2, 3 (only Grades available)
Neutrophils	Neutrophil decreased <LLN - ≥ 1.5 x10e9 /L <1.5 – ≥ 1.0 x10e9 /L <1.0 – ≥ 0.5 x10e9 /L <0.5 x10e9 /L	CTCAE grade 1-4
Hemoglobin	Hgb decreased (anemia) <LLN - ≥ 100 g/L	CTCAE grade 1-3

	<100 – ≥ 80 g/L < 80 g/L	
	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

Table 12-4 Threshold Criteria for ECGs

Ref.: CPMP 1997 guideline.

Parameter	Threshold	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	
QT/QTcF	>450 ms (Male) or >470 ms (Female) ≥500 ms Increase from baseline >10 ms Increase from baseline >20 ms Increase from baseline between 30-60 ms Increase from baseline >40 ms Increase from baseline >60 ms	

Table 12-5 Threshold Criteria for Vital Signs

Parameter	Threshold Criteria	Comments
HR	Same criteria as above in ECG category	
SBP	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	
DBP	DBP increased	809/770 analyses
	>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 ≥5 % decrease from baseline ≥10 % decrease from baseline ≥ 20% decrease from baseline	CTCAE grade 1-3

▪ Appendix H: TEAEs of Special Interest

Respiratory symptoms are defined as any TEAEs for the following 3 PTs:

- Chest discomfort
- Dyspnoea
- Respiration abnormal

Respiratory events are defined as any of the afore-mentioned respiratory symptoms, or any TEAEs for the following 4 additional PTs:

- Asthma
- Bronchial hyperreactivity
- Bronchospasm
- Wheezing

The following AE preferred terms will be selected for elevated transaminase:

- 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