VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX18-445-110 Version 1.3 (Part A Analysis)

A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes)

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Version: 1.0
Version Date of SAP: 2 Feb 2022

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1 TABLE OF CONTENTS

2 MODIFICATIONS

2.1 Modifications to the Approved Clinical Study Protocol

Not Applicable.

2.2 Modifications to the Approved Statistical Analysis Plan

This is the 1st version of Statistical Analysis Plan for the interim analysis and final analysis.

2.3 Modifications to the Approved DMC Charter

Not Applicable.

3 INTRODUCTION

VX18-445-110 (Study 110) is a Phase 3, 2-part, open-label extension study of VX18-445-104 (Study 104). For subjects who participate in both Parts A and B, the total study duration is approximately 148 weeks (from the first dose of study drug in this study), including a 96-week Treatment Period in Part A, a 48-week Treatment Period in Part B and a 4-week Safety Follow up Period. The primary objective is to evaluate the long-term safety and tolerability of VX-445 (elexacaftor, ELX)/tezacaftor (TEZ)/ivacaftor (IVA) in subjects with cystic fibrosis (CF) who are heterozygous for the *F508del* mutation and a gating (F/G) or residual function (F/RF) mutation. Safety data will be periodically reviewed by the independent data monitoring committee (DMC).

This SAP (Methods) documents the planned statistical analyses and data presentations of safety and efficacy endpoints for Part A. The SAP will be amended to include Part B prior to Part B DBL. It is based on the most recent approved clinical study protocol (CSP), the most recent approved DMC charter, the most recent approved electronic case report form (eCRF), and the most recent approved eCRF completion guidelines.

Due to the outbreak of COVID-19, 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. This SAP summarizes the additional statistical analyses that are related to these alternative measures.

The Vertex Biometrics Department 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). The SAP (Methods) will be finalized and approved prior to IA data lock. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP.

4 STUDY OBJECTIVES

4.1 Primary Objective

To evaluate the long-term safety and tolerability of ELX/TEZ/IVA in subjects with CF who are heterozygous for the *F508del* mutation and a gating (F/G) or residual function (F/RF) mutation.

4.2 Secondary Objectives

- To evaluate the long-term efficacy of ELX/TEZ/IVA
- To evaluate the pharmacodynamics (PD) of ELX/TEZ/IVA

5 STUDY ENDPOINTS

5.1 Primary Endpoint (Parts A and B)

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

5.2 Secondary Endpoints (Part A only)

- Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$)
- Absolute change in sweat chloride (SwCl)
- Absolute change in body mass index (BMI)
- Absolute change in BMI z-score
- Absolute change in body weight
- Absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain (RD) score

5.3 Exploratory Endpoints (Part A only)

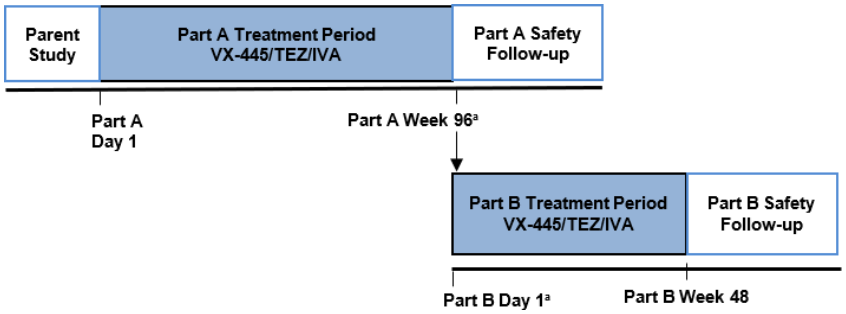
- Absolute change in CFQ-R non-respiratory domain scores
- Inflammatory mediators
- Blood biomarkers

6 STUDY DESIGN

6.1 Overall Design

This is a Phase 3, 2-part, multicenter, open-label study (OLS) for subjects who completed the last Treatment Period visit in the parent study (Study 104) and meet eligibility criteria. A schematic of the study design is shown in Figure 6-1.

Figure 6-1 VX18-445-110 Study Design



ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor
Notes: Parent study refers to Study 104. The timing of the Day 1 Visit, relative to the last scheduled visit of the parent study, is detailed in CSP Section 9.1.1. The figure is not drawn to scale.

[a] Subjects whose Part B Day 1 is on the same day or within 1 calendar day as the Part A Week 96 Visit do NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 96 Visit. Subjects whose Part B Day 1 is more than 1 calendar day after Part A Week 96 Visit must complete all assessments specified for the Part A Week 96 AND Part B Day 1 Visits.

All subjects will receive ELX/TEZ/IVA (TC) at the same dosage as that in the parent study (Study 104). The planned dosages for the Treatment Period are shown in Table 6-1.

Table 6-1 Planned Dosages

ELX Dosage	TEZ Dosage	IVA Dosage
200 mg qd	100 mg qd	150 mg q12h

ELX: elexacaftor; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor

All visits will occur within the windows specified. Please refer to Table 3-1 of the CSP for more details about study visits and assessments.

6.2 Sample Size and Power

The primary and secondary objectives of the study are the evaluation of the long-term safety and tolerability, and long-term efficacy of ELX/TEZ/IVA. This is an open-label study that will enroll subjects who complete the last Treatment Period visit in the parent study and meet eligibility criteria. The parent study is a Phase 3 Vertex study investigating ELX/TEZ/IVA (Study 104). Approximately 250 subjects are expected to enroll in this open-label study.

6.3 Randomization

Randomization is not required because all subjects will be treated identically in a single cohort.

6.4 Blinding and Unblinding

Refer to the CSP section 10.7 for details.

7 ANALYSIS SETS

The following analysis sets are defined: Open-label (OL) All Subjects Set for Part A, 104 Full Analysis Set, OL Full Analysis Set for Part A and OL Safety Set for Part A. Unless otherwise specified, all analysis sets defined in this section will be restricted to Part A data only.

7.1 OL All Subjects Set

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

7.2 104 and OL Full Analysis Set

The **Study 104 Full Analysis Set (104-FAS)** is defined the same as the FAS definition in the SAP of Study 104.

The **OL Full Analysis Set (OL-FAS) for Part A** is defined as all enrolled subjects who have received at least 1 dose of study drug in the open-label study. The OL-FAS for Part A will be used to summarize subject demographics and baseline characteristics and for all efficacy analyses unless otherwise specified.

7.3 OL Safety Set

The **OL Safety Set (OL-SS) for Part A** is defined as all subjects who received at least 1 dose of study drug in the OLS. The OL-SS for Part A will be used for all safety analyses.

8 ANALYSIS PERIOD

8.1 Parent Study Efficacy Period

The definition of this analysis period is the same as in Study 104 and will be used with the parent study efficacy analysis set (104-FAS) to analyze the efficacy data during the parent study.

8.2 Open Label Extension Period

OL Efficacy Period for Part A**:** The time from the first dose of study drug in the OLS to the last efficacy assessment, which may be collected up to the Week 96 Visit or the earlier of Day 673 and the end of study participation if subject does not have the Week 96 Visit. This analysis period will be used with the OL-FAS for Part A to analyze the efficacy data during the OLS.

OL Safety Period for Part A: The time from the first dose of study drug in the OLS to 28 days after the last dose date of the study drug in the OLS or to the completion date of study participation (defined in CSP Section 9.1.5) in Part A, whichever occurs first. This analysis period will be used with the OL-SS for Part A to analyze the safety data during the OLS.

The **Treatment-emergent (TE) Period for Part A** is same as the OL Safety Period for Part A.

Note: for subjects who depart study 110 to participate in another qualified Vertex study and return in study 110, the above defined analysis period will exclude the time between the last dose before the discontinuation from study 110 and the first dose after re-enter in study 110.

9 STATISTICAL ANALYSIS

9.1 General Considerations

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.

Data will be summarized by treatment group in the parent study (“Control in 445-104” and “ELX/TEZ/IVA in 445-104”) and overall (“Any ELX/TEZ/IVA”).

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.

Baseline value for clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry will be the TC safety baseline defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the parent study (if the subject actually received at least one dose of ELX/TEZ/IVA during the parent study) or the first dose of study drug in the OLS (if the subject did not actually receive at least one dose of ELX/TEZ/IVA during the parent study). **Baseline value** for efficacy analyses, demographics, and baseline characteristics will be the parent study baseline defined as the most recent non missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the Treatment Period 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 as (post-baseline value – baseline value)/baseline value.

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
3) In the derivation of maximum and minimum values during TE period for Part A, and maximum and minimum change from baseline values during TE period for Part A for the long-term safety analyses
4) In individual subject data listings as appropriate

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Section 12.1.

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.

Multiplicity: There will be no multiplicity adjustment as no hypothesis test is planned for safety analysis, unless specified otherwise.

9.2 Background Characteristics

9.2.1 Subject Disposition

A summary table of subject disposition in the OLS will be presented for the OL All Subjects Set for Part A by treatment group in parent study and overall with the following categories:

- Enrolled (OL All Subjects Set for Part A)
- Dosed (OL-SS for Part A)
- Enrolled and dosed (OL-FAS for Part A)

The number and percentage (based on OL-FAS for Part A) of subjects in each of the following disposition categories will be summarized by treatment group in parent study and overall:

- Completed Treatment
- Prematurely discontinued treatment and the reasons for discontinuation

- Completed study
- Prematurely discontinued the study and the reasons for discontinuation
- Rollover to Part B

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

9.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized based on the OL-FAS for Part A, and presented by treatment group in parent study and overall.

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)
- Geographic region (North America, Europe [including Australia])

Parent study baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- BMI z-score (for subjects <=20 years old at baseline)

Stratification categories used in the parent study will include the following:

- Comparator group in parent study (TEZ/IVA comparator group, IVA comparator group)
- $ppFEV_1$ at Day -14 of parent study (<70, ≥70)
- SwCl at Day -14 of parent study (<30 mmol/L, ≥30 mmol/L)

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

- $ppFEV_1$ category at baseline (<40, ≥ 40 to <70, ≥70 to ≤90, and >90)
- $ppFEV_1$ at baseline (continuous)
- Sweat chloride at baseline (continuous)
- CFQ-R respiratory domain score at 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)
- Infection with *Pseudomonas aeruginosa* within 2 years prior to screening visit of parent study (Positive, Negative)

For subjects who received TC in the parent study, prior medication use refers to medication taken during 56 days before the first dose date of study drug in the parent study treatment period or medication taken during the Run-in period. For subjects who did not receive TC in the parent study, prior medication use refers to medication taken during 56 days before the first dose date of study drug in the OLS, if applicable. No statistical tests will be carried out to evaluate any baseline imbalance between treatment groups.

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). For the OL-FAS for Part A, medical history will be summarized descriptively by treatment group in parent study and overall and by 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 (WHODrug) and categorized as follows:

- **Prior medication:** any medication that was administered during the 56 days before the first dose date of study drug in the OLS.
- **Concomitant medication:** medication continued or newly received during the TE Period for Part A for the OLS.
- **Post-treatment medication:** medication continued or newly received after the TE Period for Part A for the OLS.

A given medication may be classified as a prior medication, a concomitant medication, a post-treatment medication, both prior and concomitant, both concomitant and post-treatment, or all three categories of prior, concomitant, and post-treatment.

If a medication has completely missing or partially missing start/stop date and if it cannot be determined whether it was taken before the first dose date of the OLS, concomitantly during the TE Period for Part A for the OLS, or after the TE Period for Part A for the OLS, 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 Section 12.2.

For the OL-FAS for Part A, prior medications and concomitant medications will be summarized descriptively by: 1) treatment group in parent study and overall, Preferred Name (PN); and 2) treatment group in parent study and overall, anatomic class (ATC) level 1, ATC level 2, and PN. Post-treatment medications will be listed for each subject, if applicable.

9.2.5 Study Drug Exposure

Duration of study drug exposure (in days) will be calculated as: last dose date of study drug in the OLS – first dose date of study drug in the OLS + 1, regardless of study drug interruption. For subjects who enroll in another qualified Vertex study before completing this study and resume participation in this study, time spent in the other study will be excluded.

Study drug exposure (in weeks) during OL safety period for Part A for the OL-SS for Part A will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized into the following categories: <=24 weeks, >24 to <=48 weeks, >48 to <=72 weeks, >72 to <=96 weeks, >96 weeks. Additionally, the total study drug exposure, defined as the sum total of the study drug exposure across all subjects (in patient-weeks and patient-years), will be provided. The summary will be presented by treatment group in parent study and overall.

9.2.6 Study Drug Compliance

Study drug compliance for the OL efficacy period for Part A will be calculated as: 100 × [1 - (total number of days of study drug interruption) / (duration of study drug exposure in days)]. 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 before completing this 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 OL-FAS for Part A and presented by treatment group in parent study and overall. 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.

In addition, percentage of tablets taken during the OL efficacy period for Part A will be calculated using the following formula: 100 × [(total number of tablets dispensed) – (total number of tablets returned)] / (total number of tablets planned to be taken per day × duration of study drug exposure in days). Summary similar to those for the study drug compliance will be produced based on the OL-FAS for Part A.

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 the OL Efficacy period for Part A will be summarized descriptively based on the OL-FAS for Part A and presented by treatment group in parent studies and overall. Additionally, IPDs during the OL Efficacy period for Part A will be provided in an individual subject data listing. IPDs will be analyzed only as part of final analysis.

9.3 Efficacy Analysis

The parent study baseline will be used to calculate the change from baseline for continuous efficacy endpoints unless otherwise specified. Data of continuous endpoints at visits in the parent study will be analyzed using the same mixed-effects model for repeated measures (MMRM) approach as described in the SAP for the parent study. The resulting estimates will be identical to

what is in the CSR of the parent study. Similarly, data of continuous endpoints at visits in the OL efficacy period for Part A will be analyzed using a separate MMRM. The results obtained from the parent study and OLE efficacy period will be displayed one followed by the other.

The focus of the efficacy analysis is to characterize the long-term treatment effects using change from baseline for each treatment group in the parent study. *P* values will not be presented.

9.3.1 Analysis of Primary Efficacy Endpoint

Not applicable since efficacy is not a primary objective.

9.3.2 Analysis of Secondary Efficacy and Pharmacodynamic Endpoint

9.3.2.1 Definition of Variables

Percent predicted forced expiratory volume in 1 second ($ppFEV_1$): Percent predicted FEV_1 is the ratio of FEV_1 (L) and predicted FEV_1 (L), expressed as a percentage. The predicted FEV_1 will be calculated using the Global Lung Function Initative[1] (GLI). See Section 12.5 for more details.

Sweat chloride (SwCl): the SwCl value for a given visit will be calculated as the mean of the non-missing sweat chloride measurements obtained on the left and right arms at that visit. If one of the two arm measurements at a time point is missing, the other will be used as the mean. A volume ≥15 μL is required for an accurate determination of sweat chloride. Any results reported as having volume <15 μL will be considered missing. Any sweat chloride values reported as >160 mmol/L will be considered missing. Any sweat chloride values reported as <10 mmol/L will be imputed as 10 mmol/L.

Body mass index (BMI): the BMI at each visit is calculated using the weight and height at each visit as follows:

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height}^2\ (\text{m}^2)}$$

BMI z-score: the BMI score, adjusted for age and sex, will be referred to as BMI-for-age z-score (BMI z-score). The BMI z-score will be calculated by using Centers for Disease Control and Prevention (CDC) growth charts[2], with the age (in months) used for the calculation defined in Section 12.1.

Cystic Fibrosis Questionnaire-Revised (CFQ-R): The CFQ-R[3,4,5] is a validated CF-specific instrument that measures quality-of-life domains. This study utilizes three different versions of CFQ-R:

- CFQ-R for Children ages 12 and 13
- CFQ-R for Adolescents and Adults (subjects 14 years and older)
- CFQ-R for Parents/Caregivers (subjects 13 years and younger)

In all three versions, specific question belonging to a domain is scored 1, 2, 3, or 4. The CFQ-R domain score, e.g., physical domain score or respiratory domain score, is defined as a scaled score as follows:

$$\text{Scaled score for a domain} = 100 \times (\text{mean (scores of all questions in the domain)} - 1)/3,$$

where the score from a negatively phrased question is first reversed, i.e., reversed score = 5 – actual score, so that 1 always represents the worst condition and 4 the best condition. The

(scaled) domain score ranges from 0 (worst condition) to 100 (best condition). The scaled score for a specific domain will not be calculated if more than half of the questions in the domain have missing scores.

The (scaled) domain score from the CFQ-R for Children ages 12 and 13 and for Adolescent and Adults will be pooled within and across subjects for the analysis purpose.

9.3.2.1 Analysis Method

Absolute change from baseline in $ppFEV_1$

The MMRM for the parent study efficacy period will be same as that described in the SAP for Study 104. In the MMRM for the OL efficacy period for Part A, the absolute change from baseline in $ppFEV_1$ will be the dependent variable. The model will include treatment group (as randomized in parent study), visit, and treatment by visit interaction as fixed effects, with continuous baseline $ppFEV_1$ from parent study, continuous baseline SwCl from parent study and comparator group (IVA comparator versus TEZ/IVA comparator) as covariates.

The repeated-measures analysis will be based on the restricted maximum likelihood method assuming an unstructured covariance structure to model the within-subject errors. The denominator degrees of freedom will be based on the method proposed by Kenward-Roger[6]. If the model fails to converge due to the unstructured covariance assumption, a compound symmetry covariance structure will be used to model the within-subject errors. In the MMRM approach, assuming that the data are missing at random, no imputation of missing data will be performed.

The number of subjects, least-squares means (LS means) for absolute change from baseline at scheduled visits within each treatment group along with the corresponding standard error (SE), and 95% confidence interval (CI) will be presented. The LS means (±SE) for absolute change from baseline at each visit will also be plotted by treatment groups. For display purpose, the estimates and corresponding 95% CI obtained from both the parent study MMRM and OLS Part A will be summarized in a single summary table.

The main analysis will be conducted with the clinic spirometry data only. In addition, the descriptive statistics for raw values and absolute changes from baseline in $ppFEV_1$ by treatment group and visit will be presented for the OL efficacy period for Part A in OL-FAS for Part A.

Absolute change from baseline in SwCl

Analysis of this PD variable will be based on the same MMRM to the analysis of the absolute change from baseline in $ppFEV_1$. A descriptive summary of raw values and absolute changes from baseline will also be presented.

Absolute change from baseline in Weight, BMI and BMI Z-score (for subjects ≤20 years of age at parent study baseline)

Analysis of these variables will be based on the same MMRM to the analysis of the absolute change from baseline in $ppFEV_1$. A descriptive summary of raw values and absolute changes from baseline will also be presented.

Absolute change from baseline in CFQ-R respiratory domain score

Analysis of this variable will be based on the same MMRM to the analysis of the absolute change from baseline in ppFEV$_1$. A descriptive summary of raw values and absolute changes from baseline will also be presented.

The analysis will include pooled CFQ-R RD score assessed at clinic and at home. An additional analysis may be performed to include only the clinic assessed CFQ-R RD score, if the home assessed data are assessed to be inconsistent with the clinic assessed data.

9.3.2.1 Sensitivity and Supportive Analysis of Secondary Endpoints

No sensitivity or supportive analysis is planned for the secondary endpoints.

9.3.2.2 Subgroup Analysis

Subgroup analysis of absolute change from baseline in ppFEV$_1$ will be performed in a manner similar to that of the primary analysis of absolute change from baseline in ppFEV$_1$ for the following subgroup:

- Comparator group (TEZ/IVA comparator, IVA comparator)

A similar MMRM used for the primary analysis will be used for the subgroup analysis, where the covariate of comparator group (TEZ/IVA comparator, IVA comparator) from the MMRM will be removed. The adjusted means with 2-sided 95% confidence intervals will be provided. Note that the proposed subgroup analysis will be implemented only if there are at least 20 subjects in each treatment group. Due to potential small sample size, the results from above mentioned subgroup analysis, especially the comparison between two comparator groups, should be interpreted with caution.

9.3.3 Analysis of Additional Efficacy Variables

9.3.3.1 Additional Spirometry Variables

Summary statistics for raw values and for changes from parent study baseline of the following spirometry measurements during the OL efficacy period for Part A within OL-FAS for Part A will be presented at each visit:

- FEV$_1$:
  - Absolute change from parent study baseline in FEV$_1$ (L)
  - Relative change from parent study baseline in FEV$_1$ (%)
  - Relative change from parent study baseline in percent predicted FEV$_1$ (%)
- FVC:
  - Absolute change from parent study baseline in FVC (L)
  - Relative change from parent study baseline in FVC (%)
  - Absolute change from parent study baseline in percent predicted FVC (percentage points)
  - Relative change from parent study baseline in percent predicted FVC (%)
- FEF$_{25-75\%}$:
  - Absolute change from parent study baseline in FEF$_{25-75\%}$ (L/sec)

- Relative change from parent study baseline in $FEF_{25-75\%}$ (%)
- Absolute change from parent study baseline in percent predicted $FEF_{25-75\%}$ (percentage points)
- Relative change from parent study baseline in percent predicted $FEF_{25-75\%}$ (%)

- FEV_1/FVC:
  - Absolute change from parent study baseline in FEV_1/FVC
  - Relative change from parent study baseline in FEV_1/FVC (%)
  - Absolute change from parent study baseline in percent predicted FEV_1 / FVC
  - Relative change from parent study baseline in percent predicted FEV_1 / FVC (%)

9.4 Safety Analysis

The primary objective of the study is the evaluation of long-term safety and tolerability of TC. All safety analyses will be based on the TE Period for Part A in the OLS for subjects in the OL-SS for Part A. 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

The TC safety baseline will be used to calculate change from baseline for continuous safety endpoints.

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

9.4.1 Adverse Events

For analysis purposes, AEs will be classified as pre-treatment AEs, treatment-emergent AEs (TEAEs), or post-treatment AEs, defined as follows:

Pre-treatment AE: any AE that occurred prior to the start of the TE Period for Part A in the OLS. For subjects who enroll 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 are 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 during the TE Period for Part A in the OLS

Post-treatment AE: any AE that worsened (either in severity or seriousness) or that was newly developed after the TE period for Part A in the OLS

For AEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs started before or after study treatment start date in the OLS, the AEs will be

classified as TEAEs. Details for imputing missing or partial start dates of adverse events are described in Section 12.3.

An overview of all TEAEs for the OL-SS for Part A will be summarized for overall ("Any ELX/TEZ/IVA") 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 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 as well as the exposure adjusted event rate will be presented for the above overview table. The exposure adjusted event rate will not be presented for strongest relationship and maximum severity categories.

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

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- Related TEAEs
- Grade 3/4 TEAEs
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- TEAEs leading to death
- Serious TEAEs
- Related serious TEAEs

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 or a continuing 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 TEAE summaries; missing relationship will be considered as related and included in the related TEAE and related serious TEAE summaries.

Additional summary table will be presented for TEAEs overall in number and percentage of subjects.

- All TEAEs by PT

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

9.4.2 Clinical Laboratory Assessments

For the treatment-emergent laboratory assessments, the observed values and change from baseline values of the continuous hematology, coagulation, and chemistry results will be summarized in SI units for overall ("Any ELX/TEZ/IVA") at each visit during the TE period for Part A for the OLS.

The number and percentage of subjects with test values meeting at least 1 threshold analysis criterion event during the TE period for Part A for the OL-SS for Part A will be summarized for overall ("Any ELX/TEZ/IVA"). The threshold analysis criterion shift from baseline will also be summarized for selected laboratory parameters. The threshold analysis criteria are provided in Section 12.4.

Results of positive urine/serum pregnancy test will be listed 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, coagulation and urinalysis values will be provided. This listing will include data from both scheduled and unscheduled visits.

9.4.3 Electrocardiogram

For the following ECG measurements during the TE period for Part A for OL-SS for Part A, a summary of observed values and change from baseline values will be provided for overall ("Any ELX/TEZ/IVA") at each visit (in ms): RR interval, PR interval, QT interval, QTcF(QT corrected for HR), QRS duration, and Heart Rate (beats per minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE period for Part A for OL-SS for Part A will be summarized for overall ("Any ELX/TEZ/IVA"). The threshold analysis criteria are provided in Section 12.4.

9.4.4 Vital Signs

For the vital signs measurements during the TE period for Part A for OL-SS for Part A, the observed values and change from baseline values will be summarized for overall ("Any ELX/TEZ/IVA") at each visit. The following vital signs parameters will be summarized: 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 during the TE period for Part A for OL-SS for Part A will be summarized for overall ("Any ELX/TEZ/IVA"). The threshold analysis criteria are provided in Section 12.4.

9.4.5 Pulse Oximetry

For the percent of oxygen saturation measurements using pulse oximetry during the TE period for Part A for OL-SS for Part A, a summary of observed values and change from baseline values will be provided for overall ("Any ELX/TEZ/IVA") 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 for Part A for OL-SS for Part A will be summarized for overall ("Any ELX/TEZ/IVA").

9.4.6 Physical Examination

No tables/figures/listings will be provided for PE data.

9.4.7 Ophthalmology Examination

Ophthalmology examination results will be provided in a data listing.

9.5 Safety Supportive Analysis

9.5.1 Adverse Events of Special Interest

For this study, elevated transaminases events and rash events, as determined by MedDRA Preferred Terms in Appendix F, are considered as adverse events of special interest.

For treatment-emergent elevated transaminases events and rash events, the following categories will be summarized for overall ("Any ELX/TEZ/IVA"):

- 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 (with the first dose date of TC in the OLS 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)

9.6 Exploratory Analysis

Analyses related to the exploratory endpoints of changes in inflammatory mediators and changes in microbiology analysis from baseline will be discussed in a separate document.

9.6.1 Analysis of absolute change from baseline in CFQ-R non-respiratory domain score

Analysis of these domains will be based on an MMRM similar to the analysis of the absolute change from baseline in $ppFEV_1$. The mean plot will not be produced for these domains.

10 Interim and DMC Analyses

10.1 Interim Analysis

As mentioned in the protocol, IA for study 110 may take place at any time during the study at the discretion of the sponsor.

10.2 DMC Analysis

An independent data monitoring committee (IDMC) was formed before initiation of study 110. The IDMC's objectives and operational details are described in the IDMC charter. The IDMC will conduct regular planned safety reviews of study data as outlined in the IDMC Charter and IDMC Analysis Plan.

11 REFERENCES

[1] Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall G, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.

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

[3] Goss C, Quittner AL. Patient-reported outcomes in cystic fibrosis. Proc Am Thorac Soc. 2007;4:1-9.

[4] Modi AC, Quittner AL. Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis. J Pediatr Psychol. 2003;28(8):535-45.

[5] Quittner AL, Modi A, Cruz I. Systematic review of health-related quality of life measure for children with respiratory conditions. Pediatr Respir Rev. 2008;9:220-32.

[6] Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 1997;53:983-97.

12 APPENDICES

12.1 Analysis Visit Windows for Safety and Efficacy Assessments

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

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3,4,5]
Spirometry Weight, Height and BMI (and the corresponding z-score)[6]	Parent study baseline	--	≤1 corresponding to the first dose date of parent study
	OL Day 15	15	(1, 22]
	OL Week 4	29	(22, 43]
	OL Week 8	57	(43, 85]
	OL Week 16	113	(85, 141]
	OL Week 24	169	(141, 211]
	OL Week 36	253	(211, 295]
	OL Week 48	337	(295, 379]
	OL Week 60	421	(379, 463]
	OL Week 72	505	(463, 547]
	OL Week 84	589	(547, 631]
	OL Week 96	673	(631, 687]
	OL Safety Follow-up	Not applicable	>687
Sweat Chloride	Parent study baseline	--	≤1 corresponding to the first dose date of parent study
	OL Day 15	15	(1, 22]
	OL Week 4	29	(22, 43]
	OL Week 8	57	(43, 113]
	OL Week 24	169	(113, 253]
	OL Week 48	337	(253, 421]
	OL Week 72	505	(421, 589]
	OL Week 96	673	(589, 687]
CFQ-R	Parent study baseline	--	≤1 corresponding to the first dose date of parent study
	OL Week 4	29	(1, 43]
	OL Week 8	57	(43, 113]
	OL Week 24	169	(113, 253]
	OL Week 48	337	(253, 421]
	OL Week 72	505	(421, 589]
	OL Week 96	673	(589, 687]
	OL Safety Follow-up	Not applicable	>687

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

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3,4,5]
Hematology Serum Chemistry Vital Signs	TC safety baseline OL Day 15 OL Week 4 OL Week 8 OL Week 16 OL Week 24 OL Week 36 OL Week 48 OL Week 60 OL Week 72 OL Week 84 OL Week 96 OL Safety Follow-up	1 15 29 57 113 169 253 337 421 505 589 673 Not applicable	defined in section 8.1 [1, 22] where day 1 is postdose measurement (22, 43] (43, 85] (85, 141] (141, 211] (211, 295] (295, 379] (379, 463] (463, 547] (547, 631] (631, 687] Use nominal visit
Standard 12-lead ECG	TC safety baseline OL Day 15 OL Week 4 OL Week 8 OL Week 24 OL Week 48 OL Week 72 OL Week 96 OL Safety Follow-up	1 15 29 57 169 337 505 673 Not applicable	defined in section 8.1 [1, 22] where day 1 is postdose measurement (22, 43] (43, 113] (113, 253] (253, 421] (421, 589] (589, 687] Use nominal visit
Coagulation	TC safety baseline OL Week 4 OL Week 24 OL Week 48 OL Week 72 OL Week 96 OL Safety Follow-up	1 29 169 337 505 673 Not applicable	defined in section 8.1 [1, 99] where day 1 is postdose measurement (99, 253] (253, 421] (421, 589] (589, 687] 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 closest distance from the target day, the latest measurement will be used. For multiple measurements on the same day, unscheduled measurements will be treated as later than scheduled measurement.

[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:
a. Scheduled measurement will be treated as pre-dose observation.
b. Unscheduled measurement will be treated as post-dose observation.

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

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3,4,5]

[4] For safety Assessment, Safety Follow-up analysis visit will be based on nominal Safety Follow-up visit. If a subject doesn't have a nominal Safety Follow-up visit but has an ETT visit with study day >687, then the ETT visit will be mapped into Safety Follow-up analysis visit.

[5] For efficacy assessment, if a subject has nominal safety follow up visit with study day >687, then nominal Safety Follow-up visit will be mapped to Safety Follow-up visit; else if subject doesn't have a nominal safety follow-up visit with study day > 687 but has an ETT visit with study day >687, then the ETT visit will be mapped into Safety Follow-up analysis visit; else if there are multiple assessments with >687 then select the earliest record.

[6]Weight will also be used in the threshold analysis in which the TC safety baseline will be used to calculate change.

Derived Variables:

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) in parent study from the Vital Signs (VS) page at the Screening Visit in parent study, and add 0.5 month to convert to days.

   Obtain the informed consent date in parent study.

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

2. Age (in months) at first dose date and post-baseline visit (for use in calculation of BMI and weight z-score):

   Obtain the age at informed consent in "yy, mm" format (e.g., 24 years, 6 months) in parent study from the VS page at the Screening Visit in the parent study.

   Obtain the informed consent date in parent study.

   Then age (in months) at first dose or post-baseline visit = integer part of {[(age at informed consent (in months) in parent study + 0.5 + diff(first dose date or post-baseline visit date, informed consent date) in months in parent study]} + 0.5.

3. 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 study participation end date.

4. Electrocardiogram:

   Baseline is defined in Section 8.1. If multiple ECG measurements are obtained on the same calendar day during the TE period for Part A,

   - 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

12.2 Imputation Rules for Missing Prior/Concomitant Medication Dates

Imputation rnles for missing or partial medication stait/stop dates are defined below:

1. Missing or paiiial medication strut 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. IfDAY, Month and Year ai·e all missing, use a date before the first dose date (to impute in practical, use the pai·ent study info1med consent date).
2. Missing or paiiial 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. IfDAY, Month and yeai·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** for Pait A	**> End Date of TE Period** for Pait A
< First dose date of study drug	p	PC	PCA
c::: First dose date and End date of TE period for Pait A		C	CA
> End date of TE period for Pait A			A

P: Prior; C: Concomitant; A: Post

Same imputation mle will be implemented for missing and/or pa1iial dates of non-phaimacological treatment/procedure.

12.3 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.

12.4 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	

12.5 Details of GLI Equations for Calculating ppFEV$_1$

Percent predicted values will be calculated for parameters of FEV_1, FVC, FEV_1/FVC, and $FEF_{25\%-75\%}$ using the Quanjer GLI-2012 Regression Equations and Lookup Tables. Details of the derivation of the GLI equation are provided in the article by Quanjer et al. (2012).

The regression equations and lookup tables required to implement the Quanjer GLI-2012 predicted values are available in:

Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Quanjer GLI-2012 Regression Equation and Lookup Tables (Version 7 April 2013). Global Lung Function Initiative. [online] Available at: https://www.ers-education.org/lr/show-details/?idP=138978 [Accessed September 09, 2020].

The instructions and tools on how to implement the Quanjer GLI-2012 equations are:

Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Implementing GLI-2012 regression equations (Version 19 July 2015). Global Lung Function Initiative. [online] Available at: https://www.ers-education.org/lr/show-details/?idP=138979 [Accessed September 09, 2020].

Sanja Stanojevic. GLI-2012 - SAS Macro (Version 2, 7 April 2013). Global Lung Function Initiative. [online] Available at: https://www.ers-education.org/lr/show-details/?idP=138988 [Accessed September 09, 2020].

Data handling rule for spirometry is as follows:

- Input age and height with at least 2 decimal place
- For subjects whose age at informed consent of the parent study is >21 years, height at screening of the parent study is used regardless if height is collected at other study visits. For subjects whose age at informed consent of the parent study is <=21 years, height collected at the respective visit is used, and if the height at the respective visit is not available, the last non-missing record will be used.
- For race, map CRF race – “black or AA” to “black”, map all other CRF races (except white) to “other”; multiple checks for race in CRF are also mapped to “other”; white is a reference race in the equations and assumes 0 values for all race coefficients in the GLI equations.