1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX18-445-109 Version 1.0 (Final Analysis)

A Phase 3b, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects, Homozygous for *F508del*

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3 MODIFICATIONS

3.1 Modifications to the Approved Clinical Study Protocol

Not Applicable.

3.2 Modifications to the Approved Statistical Analysis Plan

Not Applicable. This is the 1st version of Statistical Analysis Plan.

4 INTRODUCTION

This statistical analysis plan (SAP) is based on the most recent approved clinical study protocol (CSP), the most recent approved electronic case report form (eCRF), and the most recent approved eCRF completion guidelines.

This SAP (Methods) documents the planned statistical analyses of efficacy and safety endpoints defined in the VX18-445-109 study protocol. It also documents analyses for additional efficacy and safety variables not specified in the protocol, which will provide supportive information for the scientific understanding of the drug entity.

The Vertex Biometrics Department will perform the statistical analysis of efficacy and safety data; SAS (Version 9.4 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the clinical database lock and treatment unblinding for the study. Any revisions to the approved SAP will be documented and approved in a SAP amendment prior to the clinical database lock and treatment unblinding. Any changes made to the SAP (Methods) after the clinical database lock has occurred will be documented in the clinical study report for this study.

5 STUDY OBJECTIVES

5.1 Primary Objective

To evaluate the efficacy of (ELX, VX-445)/TEZ/IVA in CF subjects, homozygous for *F508del* (F/F).

5.2 Secondary Objectives

- To evaluate the safety of ELX/TEZ/IVA
- To evaluate the pharmacodynamics (PD) of ELX/TEZ/IVA

6 STUDY ENDPOINTS

6.1 Efficacy and Pharmacodynamic Endpoints

6.1.1 Primary Endpoint

- Absolute change in CF Questionnaire-Revised (CFQ-R) respiratory domain score from baseline through Week 24

6.1.2 Key Secondary Endpoint

- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline through Week 24

6.2 Secondary Endpoints

- Absolute change in sweat chloride (SwCl) from baseline through Week 24
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry

7 STUDY DESIGN

7.1 Overall Design

This is a Phase 3b, randomized, double-blind, active-controlled, parallel-group, multicenter study. A schematic of the study design is shown in Figure 7-1.

In the TEZ/IVA Run-in Period, all subjects will receive TEZ 100 mg once daily (qd)/IVA 150 mg every 12 hours (q12h). After completing the TEZ/IVA Run-in Period, subjects will be randomized (1:1) to the ELX/TEZ/IVA group or TEZ/IVA group for the Treatment Period. Randomization will be stratified by $ppFEV_1$ determined during the TEZ/IVA Run-in Period (Day -14 assessment; <70 versus ≥70), age at the Screening Visit (<18 versus ≥18 years of age), and whether the subject is receiving CFTR modulator treatment at the Screening Visit (yes versus no). If the Day -14 $ppFEV_1$ value is not valid or not available, the most recent available $ppFEV_1$ value will be used for stratification.

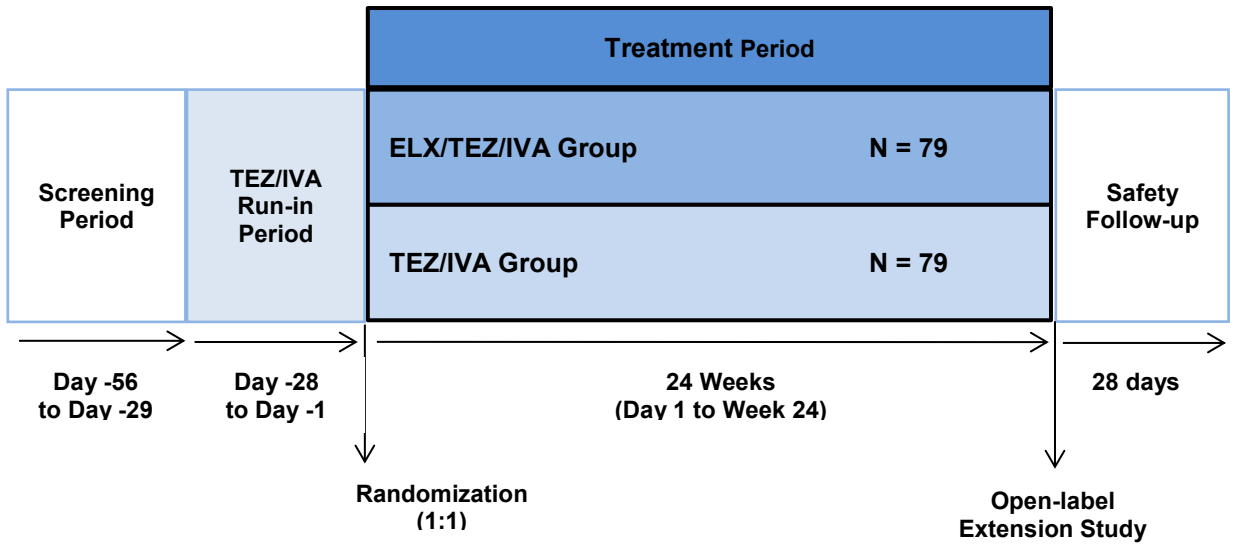
The dosages for the Treatment Period are shown in Table 7-1.

Table 7-1 Treatment Period Arms and Dosages

Treatment Arm	ELX Dosage	TEZ Dosage	IVA Dosage
ELX/TEZ/IVA	200 mg qd	100 mg qd	150 mg q12h
TEZ/IVA	0 mg	100 mg qd	150 mg q12h

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

Figure 7-1 Schematic of the Study Design



IVA: ivacaftor; N: number of subjects; TEZ: tezacaftor
Note: The Safety Follow-up Visit is not required for subjects who have enrolled in a separate open-label extension study within 28 days after the last dose of study drug after completing the Week 24 Visit.

7.2 Sample Size and Power

The primary efficacy endpoint is the absolute change in CFQ-R respiratory domain score from baseline through Week 24. The primary null hypothesis to be tested is that the mean absolute change in CFQ-R respiratory domain score from baseline is the same for the 2 treatment groups, ELX/TEZ/IVA and TEZ/IVA. The null hypothesis will be tested at a 2-sided significance level of 0.05.

Assuming a within-group SD of 18 and a treatment difference of 10 between ELX/TEZ/IVA and TEZ/IVA, a sample size of 71 subjects completing the Treatment Period in each group for a total of 142 subjects will have approximately 90% power for the CFQ-R respiratory domain score hypothesis testing, based on a 2-sample t-test at a significance level of 0.05 (2-sided). Assuming a 10% dropout rate, approximately 158 subjects will be enrolled.

The key secondary endpoint is the absolute change in $ppFEV_1$ from baseline through Week 24. Assuming a within-group SD of 7 percentage points and a treatment difference of 5 between ELX/TEZ/IVA and TEZ/IVA, a sample size of 71 subjects completing the Treatment Period in each group for a total of 142 subjects will have approximately 98% power for the ppFEV1 hypothesis testing, based on a 2-sample *t*-test at a significant level of 0.05 (2-sided).

All power calculations were based on EAST software Version 6.4.

7.3 Randomization

Randomization will be stratified by $ppFEV_1$ determined during the TEZ/IVA Run-in Period (Day -14 assessment; <70 versus ≥70), age at the Screening Visit (<18 versus ≥18 years of age), and whether the subject is receiving CFTR modulator treatment at the Screening Visit (yes versus no). If the Day -14 $ppFEV_1$ value is not valid or not available, the most recent available $ppFEV_1$ value will be used for stratification.

7.4 Blinding and Unblinding

Refer to the CSP Section 10.7 for details.

8 ANALYSIS SETS

The following analysis sets are defined: All Subjects Set, Full Analysis Set (FAS), Safety Set for the Run-in Period and Safety Set for the Treatment Period.

8.1 All Subjects Set

The **All Subjects Set** will include all subjects who are randomized or receive at least 1 dose of study drug (during either Run-in or Treatment Period). This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

8.2 Full Analysis Set

The **Full Analysis Set** (FAS) will include all randomized subjects who carry the intended *CFTR* allele mutation and receive at least 1 dose of study drug in the Treatment Period. The FAS will be used to summarize subject demographics and baseline characteristics, and for all efficacy analyses in which subjects will be analyzed according to their randomized treatment group, unless otherwise specified.

8.3 Safety Set

The **Safety Set for the Run-in Period** will include all subjects who receive at least 1 dose of TEZ/IVA in the Run-in Period. This safety set will be used for all safety analyses during the Run-in Period, and for individual subject data listings, unless otherwise specified.

The **Safety Set for the Treatment Period** will include all subjects who receive at least 1 dose of study drug in the Treatment Period. This safety set will be used for all safety analyses during the Treatment Period in which subjects will be analyzed according to the treatment they receive, unless otherwise specified.

9 STATISTICAL ANALYSIS

9.1 General Considerations

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

Categorical variables will be summarized using counts and percentages.

Baseline value, unless otherwise specified, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the Treatment Period (i.e., the Day 1 Visit). For ECG, baseline will be defined as the most recent pretreatment measurement (or the average of triplicate measurements, if the most recent pretreatment measurement is obtained in triplicate) before the first dose of study drug in the Treatment Period (i.e., the Day 1 Visit).

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.

The **Treatment-emergent (TE) Period for the Run-in Period** will be from the first dose of study drug in the Run-in Period to (1) the first dose of study drug in the Treatment Period for subjects who complete the Run-in Period and continue to the Treatment Period, or (2) 28 days after the last dose date of study drug in the Run-in Period or date of completion of study participation, whichever occurs first, for subjects who do not continue to the Treatment Period (e.g., subjects who do not meet the conditions to enter the Treatment Period).

The **TE Period for the Treatment Period** will include the time from the first dose date of study drug in the Treatment Period (ELX/TEZ/IVA or placebo + TEZ/IVA) to 28 days after the last dose of the study drug or to the date of completion of study participation, whichever occurs first.

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

1) In scheduled visit windows per specified visit windowing rules
2) In the derivation of baseline and last on-treatment measurements
3) In the derivation of maximum and minimum values during TE period, and maximum and minimum change from baseline values during TE period for safety analyses
4) In individual subject data listings as appropriate

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

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

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

9.2 Background Characteristics

9.2.1 Subject Disposition

A disposition table will be provided for the Run-in Period with the number of subjects in:

- All Subjects Set
- Safety Set for the Run-in Period

The number and percentage (based on Safety Set for the Run-in Period) of subjects in each of the following disposition categories will be summarized:

- Completed run-in period treatment
- Prematurely discontinued Run-in period treatment and the reason for treatment discontinuation
- Prematurely discontinued study during Run-in period and the reason for study discontinuation

A separate disposition table will be provided for the Treatment Period by treatment group and overall with the number of subjects in:

- Randomized
- Full Analysis Set
- Safety Set for the Treatment Period
- Randomized but not dosed in the Treatment Period

The number and percentage (based on FAS) of subjects in each of the following disposition categories will be summarized by treatment group and overall:

- Completed study drug treatment
- Prematurely discontinued treatment and the reason for discontinuation (i.e., discontinued all study drugs)
- Completed study
- Prematurely discontinued the study and the reason for discontinuation
- Rollover to the open-label study

A listing will be provided for subjects who discontinued treatment (including both the Run-in Period and Treatment Period) 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 FAS, and presented by treatment group and overall.

Demographic data will include the following:

- Age at 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, Other, and not collected per local regulations)
- Country

Baseline characteristics will include the following:

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

Stratification categories will include the following:

- Age at Screening Visit (<18, ≥18 years)
- $ppFEV_1$ at Day -14 (<70, ≥70)
- CFTR modulator use at the Screening Visit (Yes, No)

Disease characteristics will include the following:

- CFQ-R respiratory domain score at baseline (continuous)
- $ppFEV_1$ at baseline (<40, ≥ 40 to <70, ≥70 to ≤90, and >90)
- $ppFEV_1$ at baseline (continuous)
- Sweat chloride at baseline (continuous)
- Prior use of dornase alfa before the first dose of study drug in the Treatment Period (Yes, No)
- Prior use of azithromycin before the first dose of study drug in the Treatment Period (Yes, No)
- Prior use of inhaled antibiotic before the first dose of study drug in the Treatment Period (Yes, No)
- Prior use of bronchodilator before the first dose of study drug in the Treatment Period (Yes, No)
- Prior use of inhaled bronchodilator before the first dose of study drug in the Treatment Period (Yes, No)
- Prior use of inhaled hypertonic saline before the first dose of study drug in the Treatment Period (Yes, No)

- Prior use of inhaled corticosteroids before the first dose of study drug in the Treatment Period (Yes, No)
- Infection with *Pseudomonas aeruginosa* within 2 years prior to screening (Positive, Negative)

In addition, data listings will also be provided for:

- Informed consent;
- Inclusion/Exclusion criteria violation for subjects with any such violations.

9.2.3 Medical History

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). For the FAS, medical history will be summarized descriptively by System Organ Class (SOC) and Preferred Term (PT). The corresponding data listing will also be provided.

In addition, the number of subjects reported to have had positive cultures for respiratory pathogens within the 2 years prior to screening (i.e., answered yes on the respiratory microbiology form) will be summarized for the FAS. The corresponding data listing will be provided.

9.2.4 Prior and Concomitant Medications

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

Prior medication: any medication that was administered during the 56 days before the first dose of study drug in the Treatment Period but not in the Run-in Period. For subjects who discontinue during the Run-in Period and whose first dose of study drug in the Treatment Period is not available, prior medication will be any medication that was administered during the 56 days before the last dose of study drug in the Run-in Period but before the first dose in the Run-in Period.

Concomitant medication during the Run-in Period: medication continued or newly received during the TE period for the Run-in Period.

Concomitant medication during the Treatment Period: medication continued or newly received during the TE period for the Treatment Period.

Post-treatment medication: medication continued or newly received after:

- the TE period for the Run-in Period if the subject did not receive study drug in the Treatment Period.
- the TE period for the Treatment Period for subjects who received study drug in the Treatment Period.

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

If a medication has a missing or partially missing start/end date or time and if it cannot be determined whether it was taken before the first dose of study drug, concomitantly during the TE Period, or after the TE Period, it will be considered in all 3 categories of prior, concomitant, and

post treatment medication. Details for imputing missing or partial start and/or stop dates of medication are described in Appendix B.

Prior medications and concomitant medications during the Treatment Period will be summarized descriptively for FAS using frequency tables by: 1) treatment group and overall, preferred name (PN); and 2) treatment group and overall, anatomic class (ATC) level 1, ATC level 2, and PN.

The number of subjects who used hormonal therapy concomitantly will be summarized by treatment group based on the Safety Set for the Treatment Period.

Prior and concomitant medication during the Run-in Period will be summarized together in one summary table. Post-treatment medications will be listed in the all medication listing.

9.2.5 Study Drug Exposure

Study drug exposure will be summarized for the Treatment Period based on the Safety Set for the Treatment Period, and will be presented by treatment group.

Duration of study drug exposure (in weeks) will be calculated as: (last dose date of study drug in the Treatment Period – first dose date of study drug in the Treatment Period + 1)/7, regardless of study drug interruption, and will be summarized descriptively.

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

9.2.6 Study Drug Compliance

Study drug compliance will be summarized for the Treatment Period based on the FAS, and will be presented by treatment group and overall.

Study drug compliance will be calculated as: 100 × [1 - (total number of days of study drug interruption during the Treatment Period) / (duration of study drug exposure in days during the Treatment Period)]. A study drug interruption on a given day is defined as an interruption of any study drugs on that day. A study drug interruption that continues through the end of the study participation (i.e., subject does not resume study drug before the end of the study participation) will not be included in the compliance calculation.

Study drug compliance will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized in categories: <80% and ≥80% using frequency tables.

9.2.7 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. IPD rules will be developed and finalized before database lock.

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

- Subject was enrolled in the study despite the violation of inclusion/exclusion criteria
- 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

Occurrence of any of these events should be considered as potential IPDs, but a blinded team should categorize them as IPDs only if they have the potential to significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

IPDs (from the clinical database or from the site deviation log) will be summarized descriptively based on the FAS and presented by treatment group and overall. Additionally, IPDs will be provided in an individual subject data listing.

9.3 Efficacy Analysis

Unless otherwise defined, all efficacy analyses described in this section will be based on the FAS.

9.3.1 Analysis of Primary Efficacy Variable

9.3.1.1 Definition of Variable

The primary efficacy variable is the absolute change in CFQ-R respiratory domain (RD) score from baseline through Week 24.

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 for the analysis purpose.

9.3.1.2 Primary Analysis

The primary analysis will be performed using a mixed-effects model for repeated measures (MMRM) with the absolute change from baseline at each post-baseline visit as the dependent variable. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects, with continuous baseline ppFEV$_1$, age at Screening (<18 versus ≥18 years of age), and CFTR modulator use at Screening (yes versus no) as covariates. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the *F*-test for fixed

effects will be estimated using the Kenward-Roger approximation[2]. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, a compound symmetry covariance structure will be used instead. Conditional on the observed data and covariates, missing data will be assumed to be missing at random; no additional imputation of missing data will be performed.

The primary result obtained from the model will be the estimated treatment difference through Week 24 (defined as the average of Weeks 4, 8, 16, 24). The least squares (LS) mean estimate with a 2-sided 95% CI and a 2-sided P value will be provided. The treatment difference at each post-baseline visit, obtained from the model, will also be provided.

The LS mean (with SE) obtained from the MMRM analysis at each post-baseline visit up to Week 24 will be plotted by treatment group. In addition, the post-baseline raw values and the absolute change from baseline at each post-baseline visit up to Week 24 will be summarized descriptively (n, mean, SD, median, minimum, and maximum).

The primary analysis will include all available CFQ-R RD data obtained at clinic and at home. An additional analysis using data before the outbreak of COVID-19 (defined as March 2, 2020) may be performed, if the CFQ-R RD data before COVID-19 are inconsistent with CFQ-R data during COVID-19. In addition, similar additional analysis using the CFQ-R RD data obtained at clinic only may be performed, if the CFQ-R RD data obtained at home due to COVID-19 are inconsistent with the CFQ-R RD data obtained at clinic. Such additional analysis results should be interpreted with caution due to reduced sample size.

9.3.1.3 Subgroup Analysis

Subgroup analyses of the primary efficacy endpoint will be performed using a model similar to that of the primary analysis for each of the following subgroups:

- Age at Screening (<18, ≥18 years)
- $ppFEV_1$ at Baseline (< 70, ≥ 70)
- CFTR modulator use at Screening (yes, no)
- Sex (male, female)

The MMRM used for the primary analysis will be used for the subgroup analysis, where the same model will be applied to each category of the subgroup. For the subgroup analysis based on age, the covariate of age at screening (<18 versus ≥18 years) from the MMRM will be removed. For the subgroup analysis based on CFTR modulator use at Screening, the covariate of CFTR modulator use at Screening (yes, no) from the MMRM will be removed. The LS means with 2-sided 95% confidence intervals will be provided. Furthermore, the estimated treatment difference through Week 24 in different categories within a subgroup will also be presented in a forest plot. Note that the results from the subgroup analysis should be interpreted with caution in the cases where sample sizes are small.

9.3.2 Analysis of Key Secondary Variable

9.3.2.1 Definition of Variable

The key secondary efficacy variable is the absolute change in ppFEV1 from baseline through Week 24.

Percent predicted FEV_1 is the ratio of FEV_1 (L) to the predicted FEV_1 (L), expressed as a percentage. The predicted FEV_1 will be calculated using the Global Lung Function Initiative[1] (GLI); details are in Appendix C.

9.3.2.2 Analysis Method

Analysis of this variable will be based on an MMRM that is the same as the primary efficacy variable, using the spirometry data obtained at clinic only. The primary result obtained from the model will be the estimated treatment difference through Week 24 (defined as the average of Weeks 4, 8, 16, 24). Data obtained from the Day 15, Week 4, Week 8, Week 16, and Week 24 Visits will be included in the model. The Day 15 Visit will not be included in the estimation of the average treatment effect through Week 24. The least squares (LS) mean estimate with a 2-sided 95% CI and a 2-sided P value will be provided. The treatment difference at each post-baseline visit, obtained from the model, will also be provided.

The LS mean (with SE) obtained from the MMRM analysis at each post-baseline visit up to Week 24 will be plotted by treatment group. In addition, the post-baseline raw values and the absolute change from baseline at each post-baseline visit up to Week 24 will be summarized descriptively (n, mean, SD, median, minimum, and maximum).

An additional analysis may be performed to include all available spirometry data obtained at clinic and obtained at home, if the spirometry data obtained at home are assessed to be reasonably consistent with the spirometry data obtained at clinic.

9.3.2.3 Multiplicity Adjustment

A hierarchical fixed-sequence testing procedure will be used to first test the primary endpoint and then test the key secondary endpoint, in order to control the overall family-wise type I error at a 2-sided alpha of 0.05. The key secondary endpoint ($ppFEV_1$) will only be tested if the primary endpoint is statistically significant.

9.3.3 Analysis of Secondary Variable

9.3.3.1 Definition of Variable

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 <10 mmol/L or >160 mmol/L will be considered missing.

9.3.3.2 Analysis Method

Analysis of absolute change from baseline through Week 24 in sweat chloride will be based on an MMRM that is same as the primary analysis of the primary efficacy variable. The primary result obtained from the model will be the estimated treatment difference through Week 24 (defined as the average of Weeks 4, 8, 24). The LS mean estimate with a 2-sided 95% CI and a 2-sided nominal *P* value will be provided. The treatment difference at each post-baseline visit, obtained from the model, will also be provided.

The LS mean (SE) at each visit will also be plotted by treatment group. In addition, the post-baseline raw values and the absolute change from baseline at each post-baseline visit up to Week 24 will be summarized descriptively (n, mean, SD, median, minimum, and maximum).

9.4 Safety Analysis

All safety analyses will be based on data from the TE period for the Treatment Period and based on the Safety Set for the Treatment Period, unless otherwise specified. Subjects will be analyzed according to the treatment they actually received in the Treatment Period. For subjects receiving study drug from more than one treatment group, the treatment group allocation will be the higher treatment group (ELX/TEZ/IVA > 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
- ECGs
- Vital signs
- Pulse oximetry

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 pretreatment AEs, TEAEs during the Run-in Period, TEAEs during the Treatment Period, and post-treatment AEs, defined as follows:

Pretreatment AE: any AE that occurred before the first dose date of study drug (TEZ/IVA) in the Run-in Period

TEAE during the Run-in Period: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug (TEZ/IVA) through the end of the TE period for the Run-in Period

TEAE during the Treatment Period: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug (ELX or placebo+TEZ/IVA) through the end of the TE period for the Treatment Period

Post-treatment AE: any AE that worsened (either in severity or seriousness) or that was newly developed after:

- the TE period for Run-in Period if the subject did not receive treatment in the Treatment Period
- the TE period for the Treatment Period if the subject received treatment in the Treatment Period

For AEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs are pre-treatment or TEAE during the Run-in Period or post-treatment, the AEs will be classified as TEAEs corresponding to the Treatment Period. Unless otherwise specified, TEAE refers to TEAE during the Treatment Period.

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

An overview of all TEAEs by treatment group and overall will be summarized in the following categories:

- Number of TEAEs
- 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 TEAEs leading to death

The following summary tables of TEAEs will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT) using frequency counts and percentages (i.e., number and percentage of subjects with an event), and by treatment group:

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

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.

All AEs, including pretreatment AEs, TEAEs for all applicable periods, and post-treatment AEs, will be presented in an individual subject data listing based on the 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, all SAEs and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.

In addition, the following tables for the Run-in period will be presented by overall based on the Safety Set for the Run-in period.

- An overview of TEAEs during the Run-in Period
- All TEAEs during the Run-in Period by SOC and PT

9.4.1.1 Adverse Events of Special Interest

For this study, elevated transaminase 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 transaminase events and rash events, the following categories will be summarized by treatment group:

- 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

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

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

9.4.2 Clinical Laboratory

For the treatment emergent laboratory measurements, the observed values and change from baseline values of the continuous hematology, serum chemistry, and coagulation results will be summarized in SI units by treatment group at each visit.

The number and percentage of subjects meeting at least 1 threshold analysis criterion, during the TE period for Treatment Period, will be summarized by treatment group. The threshold analysis of shift from baseline will also be summarized for LFT laboratory parameters. The threshold analysis criteria are provided in Appendix E.

For selected LFT laboratory tests (alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALP], and total bilirubin), a scatter plot of the maximum treatment-emergent value versus the baseline value corresponding to ×ULN (upper limit of normal) will be

presented by treatment group. Further, a scatter plot of the maximum treatment-emergent value of ALT and AST, separately, versus the maximum treatment-emergent value of total bilirubin corresponding to ×ULN will also be presented by treatment group.

Results of urinalysis and 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, and coagulation values will be provided. This listing will include data from both scheduled and unscheduled visits.

9.4.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided at each visit by treatment group for the following ECG interval measurements (in msec): RR interval, PR interval, QT interval, QTcF interval, 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 the Treatment Period will be summarized by treatment group. The threshold analysis criteria are provided in Appendix E.

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

9.4.4 Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized at each visit by treatment group. The following vital signs parameters will be summarized: BMI (kg/m^2), weight (kg), height (cm), 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 the Treatment Period will be summarized by treatment group. The threshold analysis criteria are provided in Appendix E.

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

9.4.5 Pulse Oximetry

For the treatment-emergent oxygen saturation values by pulse oximetry, a summary of observed values and change from baseline values will be provided at each visit by treatment group.

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

9.4.6 Physical Examination

Abnormal PE findings will be presented as an individual subject data listing only.

9.4.7 Ophthalmology Examination

Ophthalmology examination results will be provided in a data listing.

9.4.8 COVID-19 Impacted Visits

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

10 Interim and DMC Analyses

10.1 Interim Analysis

Not applicable.

10.2 DMC analysis

Not applicable.

11 REFERENCES

[1] 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.

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[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] Rubin, DB. and Schenker, N.. Interval estimation from multiply-imputed data: a case study using agriculture industry codes. Journal of the American Statistical Association. 1987; 81: 366–374.

12 LIST OF APPENDICES

Appendix A: Analysis Visit Windows for Safety and Efficacy Assessment

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]
Safety Assessment			
Serum Chemistry Hematology	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 16 Week 24 Safety Follow-up	1 15 29 57 113 169 Not applicable	≤1 Pre-dose [1, 22] (22, 43] (43, 85] (85, 141] (141, 183] Use nominal visit
Standard 12-lead ECG	Day 1 (Baseline) Week 8 Week 24 Safety Follow-up	1 57 169 Not applicable	≤1 Pre-dose [1, 113] (113, 183] Use nominal visit
Vital signs and pulse oximetry (excluding BMI, Weight, Height and their Z-scores)	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 16 Week 24 Safety Follow-up	1 15 29 57 113 169 Not applicable	≤1 [1, 22] (22, 43] (43, 85] (85, 141] (141, 183] Use nominal visit
Coagulation	Day 1 (Baseline) Week 24 Safety Follow-up	1 169 Not applicable	≤1 Pre-dose [1, 183] Use nominal visit
BMI, Weight, Height and their Z-scores	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 16 Week 24 Safety Follow-up	1 15 29 57 113 169 Not applicable	≤1 (1, 22] (22, 43] (43, 85] (85, 141] (141, 183] >183
Efficacy Assessment and Pharmacodynamic Assessment			
Spirometry	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 16 Week 24 Safety Follow-up	1 15 29 57 113 169 Not applicable	≤1 Pre-dose (1, 22] (22, 43] (43, 85] (85, 141] (141, 183] >183
Sweat Chloride	Day 1 (Baseline) Week 4 Week 8 Week 24	1 29 57 169	≤1 Pre-dose (1, 43] (43, 113] (113, 183]

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]
CFQ-R	Day 1 (Baseline)	1	≤1
	Week 4	29	(1, 43]
	Week 8	57	(43, 85]
	Week 16	113	(85, 141]
	Week 24	169	(141, 183]
	Safety Follow-up	Not applicable	>183

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:

a. If no numerical measurement is available within a visit window, the measurement will be considered missing for the visit.
b. If there is more than 1 numerical measurement available within a visit window, use the following rules:
   i. The measurement closest to the target day will be used; or
   ii. If there are multiple measurements with the same distance from the target day, the latest measurement will be used.

[3] For lab, ECG and vital sign measurement collected on the date of first dose of study drug, 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.

[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 >183, then the ETT visit will be mapped into Safety Follow-up analysis visit.

[5] For efficacy assessments and nutrition variables (BMI, Weight, Height and their Z-scores), if there are multiple assessments >183, then nominal Safety Follow-up visit will be mapped to Safety Follow-up visit. If there is only ETT assessment > 183, the ETT visit will be mapped to the Safety Follow-up visit; else if there are multiple assessments with >183 then select the earliest record.

Derived Variables:

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

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

   Obtain the informed consent date.

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

2. Age (in months) at nominal visit (for use in calculation of BMI and weight z-score):

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

   Obtain the informed consent date.

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

3. Missing first dose date or last dose date

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]

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

If 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. Sweat Chloride:

   Non-missing sweat chloride concentrations from the left arm and right arm with assessment end date/time for a given arm up to 30 minutes after first dose time in treatment period will be considered for baseline.

5. Electrocardiogram:

   Baseline is defined as the most recent pretreatment measurement before the first dose of study drug in the Treatment Period. If multiple ECG measurements are obtained on the same calendar day during the TE period,

   - For summary purpose, the calculated average ECG will be used as the ECG value on that day;
   - For threshold analysis purpose, all reported ECG values will be used.

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

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

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date (in practical, use the informed consent date).
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last day of the month.
    b. If DAY and Month are both missing, use the last day of the year.
    c. If DAY, Month and year are all missing, assign 'continuing' status to stop date (in practical, use the End of Study Date 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 Run-in TE Period**	**≥ First Dose Date and < End Date of Run-in TE Period**	**≥ First Dose Date and ≤ End Date of Treatment TE Period**	**> End Date of Treatment TE Period**
< First dose date of Run-in TE period	P	PC1	PC1C2	PC1C2A
≥ First dose date and < End date of Run-in TE Period	-	C1	C1C2	C1C2A
≥ First dose date and ≤ End date of Treatment TE Period	-	-	C2	C2A
> End date of Treatment TE Period	-	-	-	A

P: Prior; C1: Concomitant during the Run-in Period; C2: Concomitant during the Treatment Period; A: Post

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

Appendix C: 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.

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: http://www.ers-education.org/home/browse-all-content.aspx?idParent=138978 [Accessed Mar 26, 2018].

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: http://www.ers-education.org/home/browse-all-content.aspx?idParent=138979 [Accessed Mar 26, 2018].

Sanja Stanojevic. GLI-2012 - SAS Macro (Version 2, 7 April 2013). Global Lung Function Initiative. [online] Available at: http://www.ers-education.org/home/browse-all-content.aspx?idParent=138988 [Accessed Mar 26, 2018].

Data handling rule for spirometry is as follows:

- Input age with at least 2 decimal place
- Use height at screening regardless if height is collected at other study visits for subjects whose age at informed consent is >21 years. For subjects with age <=21 years, height collected at the respective visit should be used; if the height at the respective visit is not available, the last non-missing record will be used.
- For race, map the CRF reported Black or African American to Black, all other races in CRF (except White) are mapped 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.

Appendix D: 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, the AE start date will be imputed using the study informed consent date.

- **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 Treatment Period or AE end date is missing, then
        - if AE start year and month are equal to the month and year of first dose date of the Treatment Period, then impute the AE start day as the day of first dose date of the Treatment Period;
        - else if AE start year and month are equal to the month and year of first dose date of the Run-in Period, then impute the AE start day as the day of first dose date of the Run-in Period;
        - else impute the AE start day as 1.
    - else if the full (or partial) AE end date is NOT before the first dose date of the Run-in Period, then
        - if AE start year and month are equal to the month and year of first dose date of the Run-in Period, then impute the AE start day as the day of first dose date of the Run-in Period;
        - else impute the AE start day as 1.
    - else 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 during the Run-in Period, TEAE during the Treatment Period, 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 of the Treatment Period or AE end date is missing, then
        - if AE start year is equal to the year of first dose date of the Treatment Period, then impute the AE start month and day as the month and day of first dose date of the Treatment Period;
        - else if AE start year is equal to the year of first dose date of the Run-in Period, then impute the AE start month and day as the month and day of first dose date of the Run-in Period;
        - else impute the AE start month as January and day as 1.
    - else if the full (or partial) AE end date is NOT before the first dose date of the Run-in Period, then
        - if AE start year is equal to the year of first dose date of the Run-in Period, then impute the AE start month and day as the month and day of first dose date of the Run-in Period;

        - else impute the AE start month as January and day as 1.
    - else 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 during the Run-in Period, TEAE during the Treatment Period, 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 and

    - 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 date of first dose date of the Treatment Period.
    - else if the full (or partial) AE end date is NOT before the first dose date of the Run-in Period, then impute the AE start date as the date of first dose date of the Run-in Period.
    - else impute AE date as the informed consent date.

The imputation should ensure the imputed AE start date is not before the informed consent date.

Imputation rules for partial AE end date are defined below:

If partial end date, then impute as min (the last day of the month, end of study participation) if day is missing, or min (Dec, end of study participation) if month is missing.

Appendix E: Criteria for Threshold Analysis

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

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

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

Parameter	Threshold Analysis	Comments
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 - ≤ 2.5xULN >2.5 – ≤ 5.0xULN >5.0 – ≤ 20.0xULN >20.0xULN	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	>1x - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Creatinine	>ULN - ≤ 1.5xULN >1.5 - ≤ 3.0xULN >3.0 - ≤ 6.0xULN >6.0xULN	CTCAE grades 1-4
Lipase	>ULN - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
Creatine kinase	>ULN - ≤ 2.5 x ULN >2.5 - ≤ 5 x ULN >5 - ≤ 10x ULN >10 x 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

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

Parameter	Threshold Analysis	Comments
Platelets	Platelet decreased <LLN - ≥ 75.0 x 10e9 /L <75.0 – ≥ 50.0 x 10e9 /L <50.0 – ≥ 25.0 x 10e9 /L <25.0 x 10e9 /L	CTCAE grade 1-4
	Platelet increased >ULN	No CTCAE available
Reticulocytes/Erythrocytes (%)	<LLN >ULN	No CTCAE
Coagulation		
Activated partial thromboplastin time (PTT)	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN	CTCAE grade 1-3

Table 12-4 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
HR	Bradycardia <50 bpm <45 bpm Decrease from baseline ≥10 bpm Decrease from baseline ≥20 bpm <50 bpm and decrease from baseline ≥10 bpm <50 bpm and decrease from baseline ≥20 bpm	Per HV grade 2, 3, plus shift change
	Tachycardia >100 bpm >115 bpm >130 bpm Increase from baseline ≥10 bpm Increase from baseline ≥20 bpm >100 bpm and increase from baseline ≥10 bpm >100 bpm and increase from baseline ≥20 bpm	Per HV grade 1, 2, 3, plus shift change
PR	≥240 ms ≥300 ms ≥200 ms and increase from baseline ≥40 ms ≥200 ms and increase from baseline ≥100 ms	
QRS	>110 ms >160 ms Increase from baseline ≥20 ms Increase from baseline ≥40 ms	

Table 12-4 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
QTc	>450 to <500ms (Male) or >470 to <500ms (Female) ≥500 ms Increase from baseline Increase from baseline >10 ms Increase from baseline >20 ms Increase from baseline >40 ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula.

Table 12-5 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
Pulse Rate	Same as above in ECG category	
SBP increased	>140 mmHg >160 mmHg >10 mmHg increase from baseline >20 mmHg increase from baseline >140 mmHg & >10 mmHg increase from baseline >140 mmHg & >20 mmHg increase from baseline >160 mmHg & >10 mmHg increase from baseline >160 mmHg & >20 mmHg increase from baseline	809/770 analyses
SBP decrease	<90 mmHg <80 mmHg >10 mmHg decrease from baseline >20 mmHg decrease from baseline <90 mmHg and >10 mmHg decrease from baseline <90 mmHg and >20 mmHg decrease from baseline <80 mmHg and >10 mmHg decrease from baseline <80 mmHg and >20 mmHg decrease from baseline	Per HV grade 1, 3, plus shift change

Table 12-5 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 ≥5 % increase from baseline ≥10 % increase from baseline ≥ 20% increase from baseline	CTCAE grade 1-3
	Weight loss ≥5 % decrease from baseline ≥10 % decrease from baseline ≥ 20% decrease from baseline	CTCAE grade 1-3

Table 12-6 Threshold Analysis Criteria for Laboratory Tests (for labeling purpose)

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

Appendix F: Adverse Events of Special Interest

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

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

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