VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX20-445-119 Version 1.0 (Final Analysis)

A Phase 3b Open-label Study Evaluating the Long-term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Cystic Fibrosis Subjects Ages 6 Years and Older Who Are Heterozygous for the *F508del* Mutation and a Minimal Function Mutation (F/MF)

Authors of SAP: [redacted]

Version: 1.0
Version Date of SAP: 22 March 2023

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

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

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

3 INTRODUCTION

Study VX20-445-119 is a Phase 3b Open-Label Extension (OLE) study evaluating the long-term safety and efficacy of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) combination therapy in subjects with cystic fibrosis who are at least 6 years of age and heterozygous for the *F508del* mutation and a minimal function mutation (F/MF).

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 VX20-445-119 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. Any revisions to the approved SAP will be documented and approved in an amendment prior to the clinical database lock.

4 STUDY OBJECTIVES

4.1 Primary Objective

To evaluate the long-term safety and tolerability of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) in subjects with CF

4.2 Secondary Objectives

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

5 STUDY ENDPOINTS

5.1 Primary Endpoint

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

5.2 Secondary Endpoints

- Absolute change in sweat chloride (SwCl) from baseline
- Absolute change in lung clearance index$_{2.5}$ ($LCI_{2.5}$) from baseline

5.3 Other Endpoints

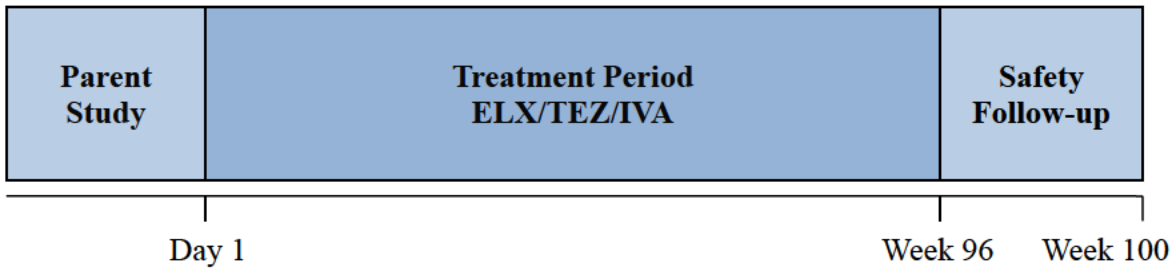
- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline

6 STUDY DESIGN

6.1 Overall Design

This is a Phase 3b, multicenter, open-label study for subjects who complete the parent study (VX19-445-116) and meet eligibility criteria. A schematic of the study design is shown in Figure 6-1.

Figure 6-1 VX20-445-119 Study Design



ELX: elexacaftor; IVA: ivacaftor, TEZ: tezacaftor

Note: Figure not drawn to scale.

Subjects will receive ELX/TEZ/IVA triple combination (TC) at the weight-appropriate dosage levels shown in Table 6-1 based on their weight at Day 1.

Table 6-1 Treatment Period Dosages

Subject Age Weight	ELX Dosage	TEZ Dosage	IVA Dosage
≥6 to <12 years			
<30 kg	100 mg qd	50 mg qd	75 mg q12h
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
≥12 years			
All weights	200 mg qd	100 mg qd	150 mg q12h

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

If a subject enters the current study weighing <30 kg and subsequently weighs ≥30 kg at 2 consecutive clinic visits (excluding unscheduled visits), the dose will be adjusted to the higher

dose of ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h for the remainder of the study, starting with the second visit where the subject's weight is ≥30 kg.

Subjects ≥12 years of age will receive a dose of ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h, starting from the first study visit at which the subject is ≥12 years old.

6.2 Sample Size and Power

The primary objective of the study is the evaluation of the long-term safety and tolerability of ELX/TEZ/IVA. This is an OLE study that will enroll subjects who did not discontinue study drug during the Treatment Period in parent study (445-116) and meet eligibility criteria. Approximately 108 subjects are expected to enroll in this OLE.

6.3 Randomization

Not applicable.

6.4 Blinding and Unblinding

Refer to the CSP Section 10 for details.

7 ANALYSIS SETS

The following analysis sets are defined: Open-label (OL) All Subjects Set, 116 and OL Full Analysis Set, and OL Safety Set.

7.1 OL All Subjects Set

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

7.2 116 and OL Full Analysis Set

The **Study 116 Full Analysis Set (116-FAS)** is defined the same as the FAS definition in the SAP of Study 116.

The **OL Full Analysis Set (OL-FAS)** will include all enrolled subjects who have received at least 1 dose of study drug in this OLE study. The OL-FAS 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)** will include all subjects who have received at least 1 dose of study drug in this OLE study. The OL-SS will be used for all safety analyses unless otherwise specified.

8 STATISTICAL ANALYSIS

8.1 General Considerations

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

The Schedule of Assessments is provided in Section 3 of CSP.

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.

The **baseline value**, unless otherwise specified, for the long-term safety analysis will be the **TC safety baseline**, defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of ELX/TEZ/IVA either in the parent study or the open label study, as applicable. The baseline value for the long-term efficacy analysis, unless otherwise specified, 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 parent study. For assessments collected in duplicate or triplicate, the baseline will be defined as the average of non-missing values.

Absolute change from baseline will be calculated as post-baseline value - baseline value.

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

Treatment-emergent (TE) Period will include the time from the first dose date of study drug in the OLE to 28 days after the last dose of the study drug in the OLE or to the date of completion of study participation (as defined in CSP Section 9.1.5), 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 otherwise specified.

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 otherwise specified.

8.2 Background Characteristics

8.2.1 Subject Disposition

A summary table of subject disposition will be presented for the OL-AS by treatment group in the parent study and overall with the following categories:

- Enrolled (OL-AS)
- Dosed (OL-SS)
- Enrolled and dosed (OL-FAS)

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

- Completed treatment
- Prematurely discontinued the treatment and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation

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

8.2.2 Demographics and Baseline Characteristics

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

Demographic data from the parent study (445-116) 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, multiracial, and not collected per local regulations)
- Country

Baseline characteristics from the parent study (445-116) will include the following:

- Weight (kg)
- Weight-for-age z-score
- Height (cm)
- Height-for-age z-score
- BMI (kg/m^2)
- BMI-for-age z-score

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

- $LCI_{2.5}$ at Screening Visit (<10, ≥ 10)
- Weight at Screening Visit (<30, ≥ 30 kg)

Disease characteristics from the parent study (445-116) baseline will include the following:

- Sweat chloride at parent study baseline (continuous)
- $LCI_{2.5}$ at parent study baseline (continuous)
- $ppFEV_1$ category at parent study baseline (<70, ≥ 70 to ≤ 90, and >90)
- $ppFEV_1$ at parent study baseline (continuous)

- CFQ-R respiratory domain score at parent study baseline (child 6-11's version, continuous)
- Prior use of dornase alfa (Yes, No)
- Prior use of azithromycin (Yes, No)
- Prior use of inhaled antibiotic (Yes, No)
- Prior use of any bronchodilator (Yes, No)
- Prior use of any inhaled bronchodilator (Yes, No)
- Prior use of any inhaled hypertonic saline (Yes, No)
- Prior use of any inhaled corticosteroids (Yes, No)

Prior medication use definition is same as that for the baseline characteristics summary presented in the parent studies. In addition, data listings will also be provided for:

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

8.2.3 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, 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.

8.2.4 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 date of study drug in this OLE study.

Concomitant medication: medication continued or newly received during the TE period in this OLE study.

Post-treatment medication: medication continued or newly received after the TE period in this OLE study.

A given medication may be classified as follows: prior, concomitant, post-treatment, both prior and concomitant, both concomitant and post-treatment, or 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 OLE, concomitantly during the TE Period for the OLE, or after the TE Period for the OLE, 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.

For the OL-SS, 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.

8.2.5 Study Drug Exposure

Duration of study drug exposure (in days) will be calculated as: last dose date of study drug in the OLE – first dose date of study drug in the OLE + 1, regardless of study drug interruption.

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 (<=24 weeks, >24 to <=48 weeks, >48 to <=72 weeks, >72 to <=96 weeks, >96 weeks), using counts and percentages. Additionally, the total study drug exposure, defined as the sum total of the study drug exposure across all subjects (in patient-years), will be provided. Exposure summaries will be based on the OL-SS, and presented overall.

8.2.6 Study Drug Compliance

Study drug compliance will be calculated as: $100 \times [1 - (\text{total number of days of study drug interruption}) / (\text{duration of study drug exposure in days})]$. A study drug interruption on a given day is defined as an interruption of any study drug on that day.

Percentage of study drug compliance will be summarized based on the OL-FAS 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.

8.2.7 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 will be summarized descriptively based on the OL-FAS and presented by treatment group in parent studies and overall. Additionally, IPDs will be provided in an individual subject data listing.

8.3 Efficacy Analysis

8.3.1 Analysis of Primary Efficacy Endpoint

Not applicable since efficacy is not a primary objective.

8.3.2 Analysis of Secondary Efficacy Endpoint

8.3.2.1 Definition of Variables

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.

Lung clearance index 2.5 ($LCI_{2.5}$): the $LCI_{2.5}$ assessments are derived from N_2-multiple-breath washout (MBW) testing. Each MBW will be performed in multiple replicates for each visit and the final $LCI_{2.5}$ value will be calculated from the technically acceptable washout replicates as graded and determined by a central reader. The following algorithm is used to derive the valid $LCI_{2.5}$ value at each visit based on the multiple attempt replicates:

- When there is only one acceptable replicate at the visit, the $LCI_{2.5}$ values will not be calculated. The assessment for that subject at the corresponding visit will be missing.
- When there are 2 or more acceptable replicates at the visit, the mean of the values for the acceptable replicates will be calculated as the $LCI_{2.5}$ value at the corresponding visit.

8.3.2.2 Analysis Method

Absolute change in SwCl from baseline:

The mixed-effects model for repeated measures (MMRM) for the parent study 116-FAS will be same as that described in the SAP for Study 116. In the MMRM for the OL-FAS, the absolute change from baseline in SwCl will be the dependent variable. The model will include treatment group (as randomized in the parent study), visit, and treatment-by-visit interaction as fixed effects, with continuous baseline $LCI_{2.5}$ from the parent study and weight at Screening (<30 versus ≥30 kg) of the parent study 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.

Results from the 2 MMRMs (for the parent study and for the OE) will be presented in a single summary table. The number of subjects, least-squares means (LS means) for absolute change from baseline at scheduled visits within each treatment group (as randomized in the parent study) 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 group (as randomized in the parent study).

In addition, the descriptive statistics for raw values and absolute changes from baseline by treatment group (as randomized in the parent study) and OL visit will be presented for the OL-FAS.

Absolute change in $LCI_{2.5}$ from baseline:

Analysis of this endpoint will be based on an MMRM similar to the analysis of the absolute change from baseline in SwCl. A descriptive summary of raw values and absolute changes from baseline will also be presented.

8.3.2.3 Sensitivity and Supportive Analysis of Secondary Endpoints

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

8.3.2.4 Subgroup Analysis

No subgroup analysis is planned for the secondary endpoints.

8.3.3 Analysis of Additional Efficacy Variables

8.3.3.1 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 Appendix C for more details.

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 four different versions of CFQ-R:

- CFQ-R for Children ages 6 to 11
- 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 four 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 6 to 11, for Children ages 12 and 13, and for Adolescent and Adults will be pooled within and across subjects for the analysis purpose.

8.3.3.2 Analysis Method

Absolute change in ppFEV$_1$ from baseline:

Analysis of this endpoint will be based on an MMRM similar to the analysis of the absolute change in SwCl. A descriptive summary of raw values and absolute changes from parent study baseline will also be presented.

The primary analysis will use the spirometry data obtained at clinic only. 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.

Absolute change in CFQ-R respiratory domain (RD) score from baseline:

Analysis of this endpoint will be based on an MMRM similar to the analysis of the absolute change in SwCl. A descriptive summary of raw values and absolute changes from parent study baseline will also be presented. In addition, the descriptive summary for raw values and the absolute change from parent study baseline of the parent version's CFQ-R RD score will be presented.

8.4 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 in the OLE for subjects in the OL-SS. 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
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry

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

8.4.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs, and post-treatment AEs, defined as follows:

- **Pretreatment AE**: any AE before the first dose of ELX/TEZ/IVA in the TE Period in this OLE study
- **TEAE**: any AE that worsened (either in severity or seriousness) or newly developed at or after the first dose date of ELX/TEZ/IVA in the TE Period in this OLE study
- **Post-treatment AE**: any AE that worsened (either in severity or seriousness) or newly developed after the TE Period in this OLE study

For AEs with missing or partial start dates, if there is no clear evidence that the AEs started before or after study drug treatment, then the AEs will be classified as TEAEs. Details for imputing missing or partial start dates of adverse events are described in Appendix D.

An overview of all TEAEs for the OL-SS during the TE Period will be summarized overall 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 treatment discontinuation
- Subjects with TEAEs leading to treatment interruption
- Subjects with Grade 3/4/5 TEAEs
- Subjects with related TEAEs
- Subjects with serious TEAEs
- Subjects with related serious TEAEs
- Subjects with TEAE leading to death

The frequency counts and percentages, as well as the exposure adjusted event rate, will be presented for the above overview table. The exposure adjusted rate will not be presented for strongest relationship and maximum severity categories.

The following summary tables of TEAEs will be presented overall:

- All TEAEs
- Grade 3/4/5 TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Related TEAEs
- Serious TEAEs
- Related serious TEAEs
- TEAEs leading to death

Summaries will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT) using frequency counts, percentages (i.e., number and percentage of subjects with an event), and the exposure adjusted event rate (except for summary by strongest relationship and maximum severity). 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 3/4/5 TEAE summaries; missing relationship will be considered as related and included in the related TEAE and related serious TEAE summaries.

An additional summary table in which the frequency counts and percentages as well as the exposure adjusted event rate will be presented for TEAEs during the OL safety period:

- All TEAEs by PT

All AEs, including pretreatment AEs, TEAEs, and post-treatment AEs, will be presented in an individual subject data listing based on the OL-AS. In addition, separate listings containing individual subject adverse event data for TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, Grade 3/4/5 TEAEs, SAEs and all deaths will be provided, with a flag indicating the TEAE status for SAEs and deaths.

8.4.1.1 Adverse Events of Special Interest

For this study, elevated transaminases events and rash events, as determined by MedDRA PTs in Appendix F, are considered as AESIs.

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

- 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 OLE as the reference while calculating time-to-onset)

8.4.2 Clinical Laboratory

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 overall at each visit during the TE Period for the OLE.

The number and percentage of subjects with test values meeting at least 1 threshold analysis criterion event during the TE Period for the OL-SS will be summarized overall. The threshold analysis shift from baseline will also be summarized for selected 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 [TBILI]), a scatter plot of the maximum treatment-emergent value versus the baseline value corresponding to ×ULN (upper limit of normal) will be presented overall. Furthermore, a scatter plot of the maximum treatment-emergent value of ALT and AST, separately, versus the maximum treatment-emergent value of TBILI corresponding to ×ULN will also be presented.

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.

8.4.3 Electrocardiogram

For the following ECG measurements during the TE Period of OL-SS, a summary of observed values and change from baseline values will be provided at each visit (in msec): RR interval, PR interval, QT interval, and 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 of OL-SS will be summarized overall. The threshold analysis criteria are provided in Appendix E.

8.4.4 Vital Signs

For the vital sign measurements during the TE Period of OL-SS, the observed values and change from baseline values will be summarized at each visit. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), 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 will be summarized. 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.

8.4.5 Pulse Oximetry

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

The number and percentage of subjects with shift changes from baseline category (classified as normal/missing or low according to the reference range) to the category at the lowest percent of oxygen saturation during the TE Period for OL-SS will be summarized. The reference range for normal oxygen saturation is specified as >95%, and <=95% for low oxygen saturation.

8.4.6 Ophthalmologic Examinations

Ophthalmologic examination results for the OL-AS will be provided in a data listing.

8.4.7 Physical Examination

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

8.4.8 COVID-19 Impacted Visits

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

9 INTERIM AND DMC ANALYSES

9.1 Interim Analysis

No interim analysis is planned at this moment; otherwise, the SAP will be amended.

9.2 DMC Analysis

An independent data monitoring committee (IDMC) was formed before initiation of study 119. 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.

10 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.

11 LIST OF APPENDICES

Appendix A: Analysis Visit Windows for Safety and Efficacy Assessment

Table 11-1 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window[2,3,4] (in study days)
Spirometry Weight, Height and BMI as well as the corresponding z-score	Parent Study Baseline	--	≤1 corresponding to the first dose date of parent study
	OL Week 4	29	(1, 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, 729]
	OL Safety Follow-up	Not applicable	Use nominal visit
Sweat Chloride, $LCI_{2.5}$, 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, 85]
	OL Week 16	113	(85, 141]
	OL Week 24	169	(141, 253]
	OL Week 48	337	(253, 421]
	OL Week 72	505	(421, 589]
	OL Week 96	673	(589, 729]
Hematology Serum Chemistry Pulse Oximetry Vital Signs (excluding Weight, Height and BMI as well as the corresponding z-score)	TC Safety Baseline	1	Defined in Section 8.1
	OL Week 4	29	[1, 43] where day 1 is post-dose measurement
	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[4]	Not applicable	Use nominal visit
Standard 12-lead ECG	TC Safety Baseline	1	Defined in Section 8.1
	OL Week 8	57	[1, 85] where day 1 is post-dose measurement
	OL Week 16	113	(85, 141]
	OL Week 24	169	(141, 253]
	OL Week 48	337	(253, 421]
	OL Week 72	505	(421, 589]
	OL Week 96	673	(589, 687]
	OL Safety Follow-up[4]	Not applicable	Use nominal visit

Table 11-1 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window[2,3,4] (in study days)
Coagulation	TC Safety Baseline	1	Defined in Section 8.1
	OL Week 24	169	[1, 253] where day 1 is post-dose measurement
	OL Week 48	337	(253, 421]
	OL Week 72	505	(421, 589]
	OL Week 96	673	(589, 687]

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. If the latest measurement cannot be determined, then unscheduled visit will be selected

[3] For measurement collected on the date of first dose of study drug in Treatment Period, if it cannot be determined whether the measurement is before or after the first dose:
a. Scheduled measurement will be treated as pre-dose observation.
b. Unscheduled measurement will be treated as post-dose observation.

[4] 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.

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

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

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

3. Missing first dose date or last dose date

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

Table 11-1 Analysis Visit Windows for Safety and Efficacy Assessments

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

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 (to impute 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 End of Study to impute).

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

Table 11-1 Prior, Concomitant, and Post Categorization of a Medication

	Medication Stop Date		
Medication Start Date	**< First Dose Date of Study Drug**	**≥ First Dose Date and ≤ End Date of TE Period**	**> End Date of TE Period**
< First dose date of study drug	P	PC	PCA
≥ First dose date and ≤ End date of TE period	-	C	CA
> End date of TE period	-	-	A

P: Prior; C: Concomitant; A: Post

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 places
- 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 study informed consent/assent date, the AE start date will be imputed using the study informed consent/assent 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 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 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 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 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 first dose date of the Treatment Period;
    - else impute the AE start date as the informed consent/assent date.

Imputation rules for partial AE end date are defined below:

- Impute the AE end date 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 11-2 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>20xULN	FDA DILI Guidance
Alkaline Phosphatase	>ULN - ≤1.5xULN >1.5 - ≤2.5xULN >2.5 - ≤5.0xULN >5.0 - ≤20.0xULN >20.0xULN	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 11-2 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 - ≤2.5xULN >2.5 - ≤5xULN >5 - ≤10xULN >10xULN	CTCAE grades 1-4
Hematology		
Hemoglobin	Hgb decreased (anemia) <LLN - ≥100 g/L <100 - ≥80 g/L <80 g/L	CTCAE grade 1-3
	Hgb increased >ULN - ≤20 g/L above ULN >20 g/L above ULN - ≤40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3
Platelets	Platelet decreased <LLN - ≥75.0 x 10e9 /L <75.0 - ≥50.0 x 10e9 /L <50.0 - ≥25.0 x 10e9 /L <25.0 x 10e9 /L	CTCAE grade 1-4

Table 11-2 Threshold Analysis Criteria for Laboratory Tests (as applicable)

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

Table 11-3 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
HR	Bradycardia ≤50 bpm	
	Tachycardia ≥140 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms	
QTc	Absolute values (ms) >450 ms (Male); >470 ms (Female) ≥500 ms Increase from baseline Increase from baseline 30-60 ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula.

Table 11-4 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
SBP	>120 mmHg	
	<70 mmHg	
DBP	>80 mmHg	
	<50 mmHg	

Appendix F: Adverse Events of Special Interest

Table 11.6 MedDRA Preferred Terms for Event of Special Interest

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

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, including adding, removing and renaming the preferred terms, will be used in the analysis of adverse events of special interest.