1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX17-659-102 Version 3.0 (Final and Interim Analysis)

A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-659 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the *F508del* Mutation and a Minimal Function Mutation (F/MF)

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4 INTRODUCTION

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

This SAP (Methods) documents the planned statistical analyses of efficacy endpoints and safety endpoints for the interim analysis (IA) and the final analysis. [redacted].

The pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of VX-659 in the population heterozygous for the *F508del* mutation and a minimal function mutation will also be evaluated in the study. Selected analyses related to sweat chloride will be documented in this SAP, other PK and PD analyses will be documented separately in the clinical pharmacology analysis plan (CPAP) for the study.

This SAP (Methods) will be finalized and approved prior to IA data lock and treatment unblinding for the IA. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP.

The Vertex Biometrics Department will perform the statistical analysis for the final analysis and prepare the analysis package for the IA; SAS (Version 9.4 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). ICON Clinical Research Limited (ICON), appointed as the independent biostatistician, will perform the IA according to the DMC SAP and present the results to the DMC. If the DMC declares that the study has crossed the efficacy boundary, a limited Vertex unblinded team (independent of the study team) may be unblinded to the study and prepare for regulatory submission(s) based on the IA.

5 STUDY OBJECTIVES

5.1 Primary Objective

To evaluate the efficacy of VX-659 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects with cystic fibrosis (CF) who are heterozygous for *F508del* and a minimal function mutation (F/MF subjects)

5.2 Secondary Objectives

- To evaluate the safety of VX-659 in TC with TEZ and IVA
- To evaluate the pharmacodynamics (PD) of VX-659 in TC with TEZ and IVA
- To evaluate the pharmacokinetics (PK) of VX-659, TEZ, and IVA when administered in TC

6 STUDY ENDPOINTS

6.1 Efficacy and Pharmacodynamic Endpoints

6.1.1 Primary Efficacy Endpoint

- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline at Week 4

6.1.2 Secondary Efficacy and Pharmacodynamic Endpoints

The key secondary endpoints are as follows:

- Absolute change in ppFEV$_1$ from baseline through Week 24
- Number of pulmonary exacerbations (PEx) through Week 24
- Absolute change in sweat chloride (SwCl) from baseline through Week 24
- Absolute change in Cystic Fibrosis Questionnaire - Revised (CFQ-R) respiratory domain score from baseline through Week 24
- Absolute change in body mass index (BMI) from baseline at Week 24
- Absolute change in SwCl from baseline at Week 4
- Absolute change in CFQ-R respiratory domain score from baseline at Week 4

Other secondary endpoints

- Time-to-first PEx through Week 24
- Absolute change in BMI z-score from baseline at Week 24 (for subjects ≤20 years of age at Baseline)
- Absolute change in body weight from baseline at Week 24

6.2 Safety Endpoints

Safety and tolerability will be evaluated via the following endpoints:

- Adverse events (AEs)
- Clinical laboratory values
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry

6.3 Pharmacokinetic Endpoint

- PK parameters of VX-659, TEZ, M1-TEZ, and IVA

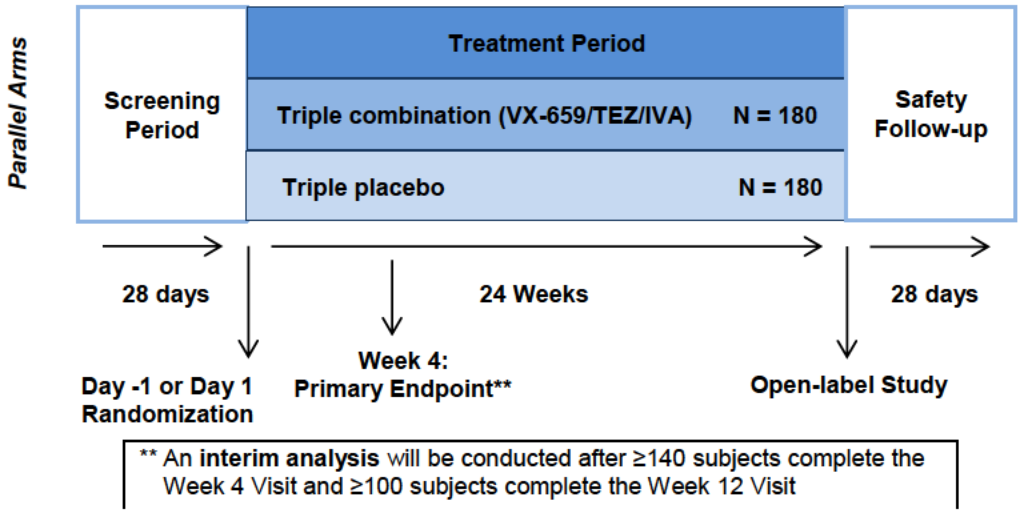
[redacted]

7 STUDY DESIGN

7.1 Overall Design

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

Figure 7-1 Schematic of the Study Design



IVA: ivacaftor; N: number of subjects; TEZ: tezacaftor
Notes: The figure is not drawn to scale. The Safety Follow-up Visit is not required for subjects who complete the Week 24 Visit and enroll in an open-label study within 28 days after the last dose of study drug (Section 9.1.3 of protocol).

Approximately 360 subjects will be randomized (1:1) to the VX-659/TEZ/IVA arm or the triple placebo arm. The planned dosages to be evaluated are shown in Table 7-1. Randomization will be stratified; details are provided in Section 9.2 of the CSP.

Table 7-1 Treatment Arms and Planned Dosages

Treatment Arm	VX-659 Dosage	TEZ Dosage	IVA Dosage
VX-659/TEZ/IVA	240 mg qd	100 mg qd	150 mg q12h
Triple placebo	0 mg	0 mg	0 mg

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

Study visits and assessments to be conducted are shown in Section 3 of CSP. All visits will occur within the windows specified.

7.2 Sample Size and Power

Approximately 360 subjects will be enrolled and randomized (1:1) to the VX-659/TEZ/IVA arm or the triple placebo arm. This sample size was determined to provide adequate power for the key secondary endpoint of the number of PEx through Week 24. Information regarding the powering of primary and selected key secondary endpoints is provided below.

Power for Primary Efficacy Endpoint

The primary efficacy endpoint is the absolute change in $ppFEV_1$ from baseline at Week 4. The primary null hypothesis to be tested is that the mean absolute change in $ppFEV_1$ from baseline is the same for the 2 treatment groups, VX-659/TEZ/IVA and placebo. If the number of subjects included in the IA is 140, the null hypothesis will be tested at a 2-sided significance level of 0.044 during the IA and at an overall 2-sided significance level of 0.05. See Section 7.5 for details on the significance level for hypothesis testing during the IA.

Assuming a within-group SD of 7 percentage points and a 5% dropout rate at Week 4, an IA sample size of 70 subjects in each treatment group will have approximately 98% power to detect a difference between the treatment groups of 5.0 percentage points for the mean absolute change in $ppFEV_1$ from baseline at Week 4, based on a 2-sided, 2-sample *t*-test at a significance level of 0.044. If the *P* value fails to cross the efficacy boundary during the IA (*P* value ≥0.044; assuming 140 subjects included in the IA), the primary endpoint of absolute change in $ppFEV_1$ from baseline at Week 4 will be tested after all subjects complete study participation at an alpha of 0.01. Assuming a 10% dropout rate at Week 24, a final analysis sample size of 180 subjects in each treatment group will have approximately 99% power to detect a difference between the treatment groups of 5.0 percentage points for the mean absolute change in $ppFEV_1$ from baseline at Week 4, based on a 2-sided, 2-sample *t*-test at a significance level of 0.01. All power calculations were based on EAST software Version 6.4.

Power for Selected Secondary Endpoints

A 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 10% dropout rate at Week 24, a sample size of 180 subjects in each treatment group will have approximately 99% power to detect a difference between the treatment groups of 5.0 percentage points for the absolute change in $ppFEV_1$ from baseline through Week 24, based on a 2-sided, 2-sample *t*-test at a significance level of 0.05.

A key secondary endpoint is the number of PEx through Week 24. Assuming a rate of PEx for the placebo group of 0.6 over 24 weeks and a 10% dropout rate, with 180 subjects and the overdispersion parameter of 0.5 in each treatment group, the power to detect a 40% reduction in the PEx rate for VX-659/TEZ/IVA group compared to placebo group is approximately 80%, based on a 2-sided, 2-sample negative binomial regression model test for the ratio of rates, at a significance level of 0.05.

7.3 Randomization

Subjects will be randomized (1:1) to the VX-659/TEZ/IVA arm or to the triple placebo arm. Randomization will be stratified by $ppFEV_1$ determined during the Screening Period (<70 versus ≥70), age at the Screening Visit (<18 versus ≥18 years of age), and sex (male versus female).

An interactive web response system (IWRS) will be used to assign subjects to treatment. The randomization code list will be produced by Vertex Biometrics or a qualified randomization vendor.

Randomization will occur before the first dose of study drug during the Treatment Period and may occur on either Day 1 or Day -1.

7.4 Blinding and Unblinding

Refer to Section 10.7 of the CSP for details.

7.5 Interim Analysis

An IA is planned when at least 140 subjects complete the Week 4 Visit and at least 100 subjects complete the Week 12 Visit. The IA will be performed by an external independent biostatistician who is not involved in and will not influence the conduct of the study, and the results will be reviewed by an independent data monitoring committee (DMC). A Lan and DeMets[3] alpha spending function will be applied to control the overall type I error rate of 0.05 for the primary endpoints during the IA and the final analysis such that an alpha of 0.01 will be preserved for the final analysis. If the number of subjects included in the IA is 140, then the primary endpoint of the absolute change from baseline in $ppFEV_1$ at Week 4 will be tested at a significance level of 0.044 during the IA. The actual alpha at the IA (α_0) will be determined based on the actual number of subjects included in the interim Full Analysis Set (see Section 8.4.1).

Table 7-2 lists the actual alpha that will be spent at the IA with various numbers of subjects included in the interim Full Analysis Set. The actual number N along with the α_0 will be communicated to the independent biostatistician and DMC approximately 5 days prior to the IA data cutoff date.

Table 7-2 The Alpha Spending with Various N at the Interim Analysis

Sample Size in interim Full Analysis Set (information fraction)	Alpha at IA (α_0)	Alpha at Final (α_1)
140 (39%)	0.0440	0.01
180 (50%)	0.0451	0.01
220 (61%)	0.0465	0.01
260 (72%)	0.0480	0.01
300 (83%)	0.0492	0.01

If the *P* value for the primary endpoint at the IA is less than α_0, then the efficacy boundary has been crossed. If the DMC declares that the study has crossed the efficacy boundary, then the study may be unblinded to a limited Vertex team to prepare regulatory submission(s). Members of the limited Vertex unblinded team will not be involved in or influence the conduct of the remaining part of the study to protect the integrity of the study.

If the *P* value fails to cross the efficacy boundary during the IA (i.e., *P* value >= α_0), then the primary endpoint of absolute change in $ppFEV_1$ from baseline at Week 4 will be tested after all subjects complete study participation at an alpha of 0.01.

Selected key secondary endpoints will be analyzed during the IA with nominal *P* value provided for descriptive purpose (see Section 10.1.3.2).

8 ANALYSIS SETS

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. 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 be defined as all randomized subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug. The FAS will be used to summarize subject demographics, baseline characteristics, and for all efficacy analyses in which subjects will be analyzed according to their randomized treatment group.

8.3 Safety Set

The **Safety Set** will include all subjects who receive at least 1 dose of study drug. The Safety Set will be used for all safety analyses in which subjects will be analyzed according to the treatment they received.

8.4 Analysis Sets for IA

A data cutoff date will be established for the IA as the latter of at least 140 subjects complete Week 4 Visit and at least 100 subjects complete Week 12 Visit.

All subjects randomized or dosed prior to the data cutoff date will be in the scope of the IA. All data reported on or before the data cutoff date will be included in the IA.

8.4.1 Interim Full Analysis Set

The **interim Full Analysis Set** (iFAS) will include subjects in the FAS whose scheduled Week 4 Visit is on or before the data cutoff date. That is, the iFAS will include subjects in the FAS who complete the Week 4 Visit or are randomized at least 28 days before the data cutoff date.

The iFAS will be used during the IA for subject demographics, baseline characteristics, and all efficacy analyses in which subjects will be analyzed according to their randomized treatment group.

8.4.2 Interim Safety Set

The **interim Safety Set** (IA Safety Set) will include subjects in the Safety Set who complete the Week 4 Visit or receive their first dose of study drug at least 28 days before the data cutoff date.

The IA Safety Set will be used during the IA for safety analyses in which subjects will be analyzed according to the treatment they received.

9 STATISTICAL ANALYSIS

This section discusses the analyses planned for the final analysis. See Section 10.1 for the analyses planned for the IA.

9.1 General Considerations

The Schedule of Assessments is provided in Section 3 of CSP. The precision standards for reporting safety and efficacy variables are provided in an internal Biometrics document that specifies the programming rules including the precision for derived variables.

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. Percentages will be presented to 1 decimal place.

Baseline value, unless otherwise specified, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the Treatment Period.

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.

Treatment-emergent (TE) period will include the time from the first dose of study drug in the Treatment Period until 28 days after the last dose of study drug or to the completion of study participation, whichever occurs first.

Completion of study participation for each individual subject is defined as one of the following:

- For subjects who complete the Treatment Period and enter an open-label study within 28 days of the Week 24 Visit: the Week 24 Visit
- For subjects who complete the Treatment Period and do not enter an open-label study within 28 days of the Week 24 Visit: the Safety Follow-up Visit
- For subjects who prematurely discontinue study drug treatment but do not withdraw consent (and assent, as applicable): the latest of the Week 24 Visit, Early Termination of Treatment Visit, or Safety Follow-up Visit (if required)
- For subjects who withdraw consent or assent: date of withdrawal of consent or assent, whichever is earlier (CSP Section 9.9)

If subjects are lost to follow-up (CSP Section 9.1.5), the date of completion of study participation will be defined as the date of the last contact.

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 otherwise specified.

9.2 Background Characteristics

9.2.1 Subject Disposition

The number of subjects in the following categories will be summarized:

- All Subjects Set
- Full Analysis Set

- Safety Set
- Randomized
- Randomized but not dosed

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

- Completed treatment
- Prematurely discontinued treatment and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation
- Rollover to open-label study

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

9.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group and overall based on the FAS.

Demographic data will include the following:

- Age at baseline (in years)
- Sex (male, female)
- 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)
- Geographic region (North America, Europe [including Israel and Australia])

Baseline characteristics will include the following:

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

Stratification categories (in addition to sex) will include the following:

- Age at the Screening Visit (<18, and ≥18 years)
- $ppFEV_1$ determined during the Screening Period (<70, and ≥70)

Disease characteristics will include the following:

- $ppFEV_1$ at baseline (<40, ≥ 40 to <70, ≥70 to ≤90, and >90)
- $ppFEV_1$ at baseline (continuous)

- Sweat chloride at baseline (continuous)
- CFQ-R respiratory domain score at baseline (continuous)
- Prior use of dornase alfa (Yes, No)
- Prior use of azithromycin (Yes, No)
- Prior use of inhaled antibiotic (Yes, No)
- Prior use of any bronchodilator (Yes, No)
- Prior use of any inhaled bronchodilator (Yes, No)
- Prior use of any inhaled hypertonic saline (Yes, No)
- Prior use of any inhaled corticosteroids (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. Hospitalization and clinic visit history in the year prior to the signing of informed consent will be listed.

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, regardless of when it ended.

Concomitant medication: medication continued or newly received on or after the first dose date of study drug through the end of the TE period.

Post-treatment medication: medication continued or newly received after the TE period.

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 a completely missing or partially missing start/stop date and it cannot be determined whether it was taken before the first dose date of study drug, concomitantly during

the TE period, or after the TE period, it will be classified as prior, concomitant, and post-treatment.

For the FAS, prior medications and concomitant medications will be summarized descriptively 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. Post-treatment medications will be listed for each subject.

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

9.2.5 Study Drug Exposure

Duration of study drug exposure (in days) will be calculated as: last dose date of study drug – first dose date of study drug + 1, 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 in categories for Treatment Period: ≤1 week, >1-≤2 weeks, >2-≤4 weeks, >4-≤8 weeks, >8-≤12 weeks, >12-≤16 weeks, >16-≤20 weeks, >20-≤24 weeks, and >24 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-weeks and patient-years), will be provided.

Exposure summaries will be based on the Safety Set, and presented by treatment group and overall.

9.2.6 Study Drug Compliance

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

Percentage of study drug compliance will be summarized based on the FAS, and presented by treatment group and overall. Percentage of study drug compliance will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized in categories: <80% and ≥80% using frequency tables.

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

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 prior to the IA data 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 reason
- Subject received prohibited concomitant medications
- Subject received the wrong treatment or incorrect doses
- Subject remained in the study despite meeting withdrawal criteria

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

All efficacy analyses described in this section will be based on the FAS, unless otherwise specified.

9.3.1 Analysis of Primary Efficacy Variable

9.3.1.1 Definition of Variables

The primary efficacy variable is the absolute change in ppFEV$_1$ from baseline at Week 4. Percent predicted FEV$_1$ is the ratio of FEV$_1$ (L) and predicted FEV$_1$ (L), expressed as a percentage. See Appendix C for more details.

9.3.1.2 Primary Analysis

The primary analysis will be performed using a mixed-effects model for repeated measures (MMRM) with change from baseline at Day 15, Week 4, Week 8, Week 12, Week 16, and Week 24 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 sex (male versus female) 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; consequently, no imputation of missing data will be performed.

The primary result obtained from the model will be the estimated treatment difference at Week 4. The adjusted means with 2-sided 95% confidence intervals and 2-sided *P* values will be provided. Furthermore, the treatment difference at each post-baseline visit obtained from the model will also be provided.

[redacted]

9.3.2 Analysis of Key Secondary Variables

9.3.2.1 Definition of Variables

Pulmonary exacerbation (PEx): A PEx is defined as a new event or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the following signs/symptoms:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature above 38°C (equivalent to approximately 100.4°F)
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination (PE) of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

The **PEx analysis period** will include the time from the first dose date of study drug until the last efficacy assessment, which may be collected up to the Week 24 Visit or the earlier of Day 169 and the end of study participation if subject does not have the Week 24 Visit.

The number of PEx through Week 24 is then defined as the total number of PEx for each treatment group during the PEx analysis period.

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.

Cystic Fibrosis Questionnaire-Revised (CFQ-R): The CFQ-R[1,4,6] 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.

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

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

9.3.2.2 Analysis Method

Absolute change in $ppFEV_1$ through Week 24: Analysis of this variable will be based on an MMRM that is exactly the same as the primary efficacy variable. However, the Day 15 Visit will not be included in the estimation of the average treatment effect through Week 24 as the treatment effect is not expected to reach the steady state at Day 15.

Number of PEx through Week 24: Analysis of this variable will be performed using a negative binomial regression model with a fixed effect for treatment, as well as continuous baseline $ppFEV_1$, age at screening (<18 versus ≥18 years of age), and sex (male versus female) as covariates. The logarithm of the subject-specific PEx analysis period duration (in years) will be treated as the offset in the model.

Absolute change in SwCl from baseline through Week 24: Analysis of this PD variable will be based on an MMRM similar to the analysis of the primary efficacy variable. Data obtained from Week 4, Week 8, Week 12, and Week 24 Visits will be included in the model and all of these visits will be included in the estimation of the average treatment effect through Week 24.

Absolute change in the CFQ-R respiratory domain score from baseline through Week 24: Analysis of this domain will be based on an MMRM similar to the analysis of the primary efficacy variable. Data obtained from Week 4, Week 8, Week 12, Week 16, and Week 24 Visits will be included in the model and all of these visits will be included in the estimation of the average treatment effect through Week 24.

Absolute change in BMI from baseline at Week 24: Analysis of this variable will be based on an MMRM similar to the analysis of the primary efficacy variable. Data obtained from Day 15, Week 4, Week 8, Week 12, Week 16, and Week 24 Visits will be included in the model.

Absolute change in SwCl from baseline at Week 4: Analysis of this PD variable will be based on an MMRM similar to the analysis of the primary efficacy variable. Data obtained from Week 4, Week 8, Week 12, and Week 24 Visits will be included in the model to estimate the treatment effect at Week 4.

Absolute change in CFQ-R respiratory domain score from baseline at Week 4: Analysis of this domain will be based on an MMRM similar to the analysis of the primary efficacy variable.

Data obtained from Week 4, Week 8, Week 12, Week 16 and Week 24 Visits will be included in the model to estimate the treatment effect at Week 4.

To assess the longitudinal profile of the efficacy and pharmacodynamic assessments with repeated measures up to Week 24, the LS mean (SE) of the within-treatment group change from baseline at each post-baseline visit along with the 95% CI will be estimated from the corresponding MMRM. The LS mean (SE) of the treatment difference between VX-659/TEZ/IVA and triple placebo at each post-baseline visit will be provided along with the corresponding 95% CI and *P* value. 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 will be summarized descriptively (n, mean, SD, median, minimum, and maximum).

9.3.2.3 Multiplicity Adjustment

The Lan and DeMets[3] alpha spending function will be applied to the primary endpoint of the absolute change in $ppFEV_1$ at Week 4 to control the overall type I error rate of 0.05 such that an alpha of 0.01 will be preserved for the final analysis.

If the number of subjects included in the IA is 140, the primary endpoint of the absolute change from baseline in $ppFEV_1$ at Week 4 will be tested at an alpha of 0.044 during the IA. The actual alpha at the IA (α_0) will be determined based on the actual number of subjects included in the interim Full Analysis Set. If the study does not cross the efficacy boundary during the IA (*P* value $\geq \alpha_0$), then the primary endpoint will be tested at an alpha of 0.01 at the final analysis when all subjects complete the study participation. See Section 7.5 for more details.

The key secondary endpoints will be formally tested at an alpha of 0.05 at the final analysis when all subjects complete study participation only if the primary endpoint is statistically significant at the IA or at the final analysis. A hierarchical testing procedure will be used to control the type I error rate for the multiple key secondary endpoints tested at an alpha of 0.05. For a test at any step to be considered statistically significant within the testing hierarchy, it must be statistically significant, and all previous tests (if any) within the hierarchy must be statistically significant at the 0.05 level. The testing order of the key secondary endpoints is as follows:

- Absolute change in $ppFEV_1$ from baseline through Week 24
- Number of PEx through Week 24
- Absolute change in SwCl from baseline through Week 24
- Absolute change in CFQ-R respiratory domain from baseline through Week 24
- Absolute change in BMI from baseline at Week 24
- Absolute change in SwCl from baseline at Week 4
- Absolute change in CFQ-R respiratory domain score from baseline at Week 4

9.3.3 Analysis of Other Secondary Variables

9.3.3.1 Definition of Variables

Time-to-first PEx through Week 24: the number of days from the first dose date of study drug to the date of the first pulmonary exacerbation during the PEx analysis period. A subject who does

not experience a PEx during the PEx analysis period will be censored at the PEx analysis period end date.

BMI z-score: the BMI score, adjusted for age and sex, will be referred to as BMI-for-age z-score (BMI z-score). The BMI z-score will be calculated by using Centers for Disease Control and Prevention (CDC) growth charts[8], with the age (in months) used for the calculation defined in Appendix A.

9.3.3.2 Analysis Method

Time-to-first PEx through Week 24: Time-to-first PEx will be analyzed using the Cox regression model. The model will include a fixed effect for treatment, as well as continuous baseline ppFEV$_1$, age at screening (<18 versus ≥18 years of age), and sex (male versus female) as covariates. Additionally, the Kaplan-Meier method will be used to produce a graphical presentation of the cumulative exacerbation-free rate for each treatment group and to estimate the cumulative exacerbation-free rate by treatment group.

Note: If the number of events is <5 in either treatment group, Cox regression will not be performed and the analysis of the time-to-first event will be restricted to the Kaplan-Meier method.

Absolute change in BMI z-score from baseline at Week 24 (for subjects ≤20 years of age at Baseline): Analysis of this variable will be based on an MMRM similar to the analysis of the primary efficacy variable, excluding the covariate of age at screening (<18 versus ≥18 years of age), for subjects ≤20 years of age at Baseline. Data obtained from Day 15, Week 4, Week 8, Week 12, Week 16, and Week 24 Visits will be included in the model.

Absolute change in body weight from baseline at Week 24: Analysis of this variable will be based on an MMRM similar to the analysis of the primary efficacy variable. Data obtained from Day 15, Week 4, Week 8, Week 12, Week 16, and Week 24 Visits will be included in the model.

[redacted]

[redacted]

9.4 Safety Analysis

All safety analyses will be based on data from the TE period for all subjects in the Safety Set. 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 (VX-659/TEZ/IVA > TC Placebo).

The overall safety profile of the 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, or post-treatment AEs, defined as follows:

Pretreatment AE: any AE that occurred before the first dose date of study drug

TEAE: any AE that worsened (either in severity or seriousness) or that was newly developed on or after the first dose date of study drug through the end of the TE period

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

For AEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs started before or after study treatment, the AEs will be classified as TEAEs.

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

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

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

The following summary tables of TEAEs will be presented 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

Summaries will be presented by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentages of subjects, subjects with multiple occurrences of the same adverse event or a continuing adverse event will be counted once, and only the maximum severity level will be presented in the severity summaries, and the strongest relationship level in the relationship summaries.

Additional summary tables will be presented by treatment for TEAEs showing number and percentage of subjects

- 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 All Subjects Set. In addition, a listing containing individual subject adverse event data for TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, Grade 3/4 TEAEs, SAEs and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.

For all AEs, the eCRF captures the action taken for VX-659/TEZ/IVA pills separately from the action taken for IVA monotherapy pills. As a result, it is possible that, in the final database (after database lock), the AE actions taken for the two agents (fixed dose VX-659/TEZ/IVA and ivacaftor monotherapy) are different. The summaries and listings of "AE Leading to Treatment Dis continuation" and "AE Leading to Treatment Interruption" account for discontinuation and interruptions for either agent.

[redacted]

9.4.2 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 at each visit by treatment group.

The number and percentage of subjects meeting at least 1 threshold analysis criterion event during the TE period will be summarized by treatment group and overall. The threshold analysis

criterion shift from baseline will also be summarized for selected laboratory parameters. The threshold analysis criteria are provided in Appendix F.

For select 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. 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 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 measurements (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 will be summarized by treatment group and overall. The threshold analysis criteria are provided in Appendix F.

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: 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 by treatment group and overall. The threshold analysis criteria are provided in Appendix F.

9.4.5 Pulse Oximetry

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

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

9.4.6 Physical Examination

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

[redacted]

10 SUMMARY OF INTERIM AND DMC ANALYSIS

For each DMC meeting and the planned IA, the Vertex Biometrics Department will prepare the analysis package using the dummy treatment code and dummy spirometry and SwCl data according to the DMC charter and the DMC SAP, respectively; SAS (Version 9.4, or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets).

ICON Clinical Research Limited (ICON), appointed as the independent biostatistician, will perform the IA according to the DMC SAP using the SAS code provided by Vertex Biometrics Department, the unblinded treatment code, the real (restricted) spirometry, and the real (restricted) sweat chloride data. Unblinded treatment code, spirometry, and sweat chloride data will be transferred directly from relevant vendors to the independent biostatistician. ICON will present the results to the DMC.

If the study crosses the efficacy boundary according to the pre-specified criterion (Section 7.5), a limited Vertex unblinded team may be unblinded to the study. The limited Vertex unblinded team will use the unblinded treatment code and real (restricted) data to generate statistical outputs and prepare for submission(s). Members of the limited Vertex unblinded team will not be involved in or influence the conduct of the remaining part of the study to protect the integrity of the study.

10.1 Interim Analysis

10.1.1 General Consideration

Refer to Section 7.5 for the timing of the IA. General considerations, reporting conventions, and analysis methods specified for the final analysis apply to the IA, unless otherwise specified.

For the IA purpose, the **treatment-emergent (TE) period** will include the time from the first dose of study drug in the Treatment Period until 28 days after the last dose of study drug, or the study participation end date, or the IA data cutoff date, whichever occurs first.

10.1.2 Background Characteristics

10.1.2.1 Subject Disposition

The number of subjects in the following categories will be summarized:

- All Subjects Set
- Interim Full Analysis Set
- IA Safety Set
- Safety Set
- Randomized
- Randomized but not dosed

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

- Completed Week 4 Visit
- Prematurely discontinued treatment before Week 4 Visit and the reason for discontinuation
- Completed Week 12 Visit
- Prematurely discontinued treatment before Week 12 Visit and the reason for discontinuation
- Completed treatment
- Prematurely discontinued treatment and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation
- Rollover to open-label study

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

10.1.2.2 Demographics and Baseline Characteristics

The same demographics and baseline characteristics specified in Section 9.2.2 will be summarized based on the iFAS.

10.1.2.3 Study Drug Exposure

For the purpose of the IA, the study drug exposure will be calculated using the same approach specified in Section 9.2.5. For subjects who are still on study drug at the IA data cutoff date, the IA data cutoff date will be used as the last dose date for the exposure calculation.

Exposure summaries will be provided for subjects in the IA Safety Set as well as for subjects in the Safety Set who had been on-study for ≥12 weeks, and will be presented by treatment group and overall.

10.1.3 Efficacy Analysis

All efficacy analyses described in this section will be based on the iFAS, unless otherwise specified.

10.1.3.1 Analysis of Primary Efficacy Variable

The analysis of the primary efficacy variable of absolute change in $ppFEV_1$ from baseline at Week 4 will be performed using an MMRM with change from baseline at Day 15 and Week 4 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 sex (male versus female) 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; consequently, no imputation of missing data will be performed.

[redacted]

10.1.3.2 Analysis of Key Secondary Efficacy Variable

The following key secondary efficacy variables defined in Section 9.3.2.1 will be analyzed during the IA using an ANCOVA model:

- Absolute change in SwCl from baseline at Week 4
- Absolute change in CFQ-R respiratory domain score from baseline at Week 4

The model will use the change from baseline value at Week 4 as the dependent variable and include treatment group as fixed effects with continuous baseline ppFEV$_1$, age at screening (<18 versus ≥18 years of age), and sex (male versus female) as covariates. The estimated treatment difference at Week 4, the adjusted means with 2-sided 95% confidence intervals and nominal 2-sided *P* values will be provided.

Analyses of other efficacy and/or pharmacodynamic variables may be performed if the data are deemed sufficient.

10.1.3.3 Summary of Efficacy Variables

The raw and change from baseline in ppFEV$_1$, SwCl and CFQ-R will be summarized descriptively (n, mean, SD, median, minimum, and maximum) at baseline and post-baseline visits. For the IA purpose, a visit will be included in the summary if there are ≥20 subjects with available data from each treatment group at that visit.

10.1.4 Safety Analysis

Safety analyses specified in Section 9.4 will be performed during the IA based on the IA Safety Set.

[redacted]

10.2 DMC Analysis

The DMC will conduct planned safety/efficacy review(s) of study data as outlined in the DMC charter. For the open session of each DMC meeting, selected tables will be presented for the overall treatment group based on the blinded data. For the closed session, the presentation will be by treatment group based on the unblinded data (generated by the independent biostatistician).

The timing of DMC meetings is outlined in Table 10-1.

Table 10-1 DMC Meeting Schedule

Meeting	Timing
Organizational	Teleconference prior to start of the study
First Planned Review	After ≥50 subjects have completed Week 4
Second Planned Review	Interim analysis of safety and efficacy after ≥140 subjects have completed the Week 4 visit and after ≥ 100 subjects have completed the Week 12 visit.
Ad-hoc	Teleconference on an as-needed basis

10.2.1 DMC Safety/Efficacy Review

To protect the integrity of the treatment assignment and study data, the following steps for the flow of data will be executed for the DMC review:

1. The Vertex Biometrics Department will prepare the SAS codes, SDTM/ADaM data sets, and blinded outputs (tables, figures and listings) of safety data using dummy treatment codes, dummy (unrestricted) spirometry data, and dummy (unrestricted) sweat chloride data;
2. The IWRS vendor, Bracket, will provide the unblinded treatment codes to the independent biostatistician via a secure file transfer protocol, the independent biostatistician will verify the treatment assignment against the randomization list generated by Cytel;
3. The spirometry vendor will provide the restricted spirometry data directly to the independent biostatistician, via a secure file transfer protocol;
4. The sweat chloride vendor will provide the restricted sweat chloride data directly to independent biostatistician, via a secure file transfer protocol;
5. Independent biostatistician will generate the unblinded outputs (tables, figures and listings) and provide them directly to the DMC team for their review, via a secure file transfer protocol.
6. The Vertex Biometrics Department will generate any blinded outputs (tables, figures and listings), for the open sessions of the DMC meetings, as applicable.

11 REFERENCES

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

12 LIST OF APPENDICES

Appendix A: Analysis Visit Windows for Safety and Efficacy Assessments

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

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3]
Safety Assessment			
Serum Chemistry Hematology Standard 12-lead ECG	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 12 Week 16 Week 24 Safety Follow-up	1 15 29 57 85 113 169 Not applicable	≤1 Pre-dose [1, 22] (22, 43] (43, 71] (71, 99] (99, 141] (141, 183] Use nominal visit
Vital Signs	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 12 Week 16 Week 24 Safety Follow-up	1 15 29 57 85 113 169 Not applicable	≤1 [1, 22] (22, 43] (43, 71] (71, 99] (99, 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
Efficacy Assessment and Pharmacodynamic Assessment			
Spirometry	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 12 Week 16 Week 24 Safety Follow-up	1 15 29 57 85 113 169 Not applicable	≤1 Pre-dose (1, 22] (22, 43] (43, 71] (71, 99] (99, 141] (141, 183] >183
Sweat Chloride	Day 1 (Baseline) Week 4 Week 8 Week 12 Week 24	1 29 57 85 169	≤1 Pre-dose (1, 43] (43, 71] (71, 127] (127, 183]
CFQ-R	Day 1 (Baseline) Week 4 Week 8 Week 12 Week 16 Week 24 Safety Follow-up	1 29 57 85 113 169 Not applicable	≤1 (1, 43] (43, 71] (71, 99] (99, 141] (141, 183] >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]
Weight, Height and BMI (and the corresponding z-score)	Day 1 (Baseline)	1	≤1
	Day 15	15	(1, 22]
	Week 4	29	(22, 43]
	Week 8	57	(43, 71]
	Week 12	85	(71, 99]
	Week 16	113	(99, 141]
	Week 24	169	(141, 183]
	Safety Follow-up	Not applicable	>183

[redacted]

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.

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 post-baseline visit date, informed consent date) 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.

   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

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]

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 Jan. 01, 2000 to impute).
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last day of the month.
    b. If DAY and Month are both missing, use the last day of the year.
    c. If DAY, Month and year are all missing, assign 'continuing' status to stop date (in practical, use Dec. 31, 2050 to impute).

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

Table 12-2 Prior, Concomitant, and Post Categorization of a Medication

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

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$_1$, [redacted] 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 and height 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 E: 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 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 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 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.
    - For the IA purpose, if the end of study date is missing, then the IA data cutoff date will be used instead in the imputation

Appendix F: 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>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.
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	FDA DILI Guidance Jul 2009.

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

Parameter	Threshold Analysis	Comments
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
	Platelet increased >ULN	No CTCAE available
Reticulocytes/Erythrocytes (%)	<LLN >ULN	No CTCAE

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

Parameter	Threshold Analysis	Comments
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 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	
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
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

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VERTEX PHARMACEUTICALS INCORPORATED

Addendum to Statistical Analysis Plan (Methods)

Protocol Number VX17-659-102 Version 3.0 (Final and Interim Analysis)

A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-659 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the *F508del* Mutation and a Minimal Function Mutation (F/MF)

Authors of SAP: [redacted]

Version: 1.0
Version Date of Addendum: 9 OCT 2018
Version Date of SAP: 14 MAY 2018

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VERTEX PHARMACEUTICALS INCORPORATED

Addendum 2 to Statistical Analysis Plan (Methods)

Protocol Number VX17-659-102 Version 3.0 (Final Analysis)

A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-659 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the *F508del* Mutation and a Minimal Function Mutation (F/MF)

Authors of Addendum 2: [redacted]

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5.2 Efficacy Analysis

5.2.1 Analysis of Endpoints Based on the Number of Clinical Events

Number of Pulmonary Exacerbation (PEx) through Week 24: The analysis pre-specified in the protocol based on the negative binomial regression model will be performed first. If the negative binomial regression does not converge, the analysis will be performed using the Poisson regression with the same covariates and offset.

Note: If the number of events is less than 5 in either treatment group, neither the negative binomial regression nor the Poisson regression will be performed and analysis of event counts will be based on a Fisher's Exact test.

Analysis of the number of PEx requiring hospitalization and/or IV antibiotics therapy, the number of planned hospitalizations for CF, and the number of unplanned hospitalizations for reasons other than antibiotic therapy for sinopulmonary signs/symptoms will be performed in the same manner.