VERTEX

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan Methods

Protocol Number VX14-661-106, Version 4.0

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of tezacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

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3 INTRODUCTION

This SAP, which describes the planned final analyses for Study VX14-661-106, is based on the following:

- the approved clinical study protocol (Version 4.0, dated 06 May 2016),
- the approved electronic case report forms (eCRF) (Version 3.0, dated 14 October, 2015).

Study VX14-661-106 is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of tezacaftor in combination with ivacaftor (TEZ/IVA) in subjects aged 12 years and older with cystic fibrosis (CF), homozygous for the *F508del* mutation on the *cystic fibrosis transmembrane conductance regulator (CFTR)* gene *(F508del-CFTR* mutation).

This SAP (Methods) documents the planned final statistical analyses of efficacy and safety endpoints defined in the VX14-661-106 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 pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of TEZ/IVA in the *F508del* homozygous population also will be evaluated in the study. The relevant PK and PD analyses, however, will not be documented in this SAP. Rather, PK and PD analyses will be documented separately in the clinical pharmacology analysis plan (CPAP) for the study.

In addition, some exploratory endpoints were described in the study protocol. Analyses of exploratory endpoints are outside of the scope of this SAP and will be documented separately.

The Vertex Biometrics Department will perform the statistical analysis of the efficacy and safety data; SAS (Version 9.2, 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 final clinical data lock and treatment unblinding for the study. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of TEZ/IVA through Week 24 in subjects with CF who are homozygous for the *F508del* mutation on the *CF transmembrane conductance regulator* (*CFTR*) gene.

4.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the safety of TEZ/IVA through Week 24

- To investigate the pharmacokinetics (PK) of tezacaftor and its metabolites, M1 and M2 (M1-661 and M2-661, respectively), and of ivacaftor and its metabolite, M1 (M1-ivacaftor).

5 STUDY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoint

The primary endpoint is absolute change from baseline in percent predicted forced expiratory volume in 1 second (FEV1) through Week 24.

5.1.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

- Relative change from baseline in percent predicted FEV1 through Week 24
- Number of pulmonary exacerbations through Week 24
- Absolute change in body mass index (BMI) from baseline at Week 24
- Absolute change in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline through Week 24

The following are other secondary efficacy endpoints:

- Time-to-first pulmonary exacerbation through Week 24
- Absolute change in sweat chloride from baseline through Week 24
- Absolute change in BMI z-score from baseline at Week 24 (in subjects <20 years of age at time of screening)
- Absolute change in body weight from baseline at Week 24

5.2 Safety Endpoints

Safety and tolerability are secondary endpoints which will be evaluated as follows:

- Adverse events (AEs)
- Clinical laboratory values (hematology, serum chemistry, coagulation studies, vitamin levels, lipid panel, and urinalysis)
- Standard 12-lead electrocardiograms (ECGs)
- Vital signs
- Pulse oximetry
- Spirometry

5.3 Pharmacokinetic Endpoints

PK parameters are secondary endpoints, which will be assessed based on the PK of tezacaftor, M1-661, M2-661, ivacaftor, and M1-ivacaftor.

[redacted]

6 STUDY DESIGN

6.1 Overview of Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in subjects with CF who are homozygous for the *F508del-CFTR* mutation. This study is designed to evaluate the efficacy and safety of TEZ/IVA. The active treatment regimen will be comprised of a morning dose of a fixed-dose combination tablet of 100 mg tezacaftor/150 mg ivacaftor once daily (qd) and an evening dose of ivacaftor 150 mg to be taken approximately 12 hours after the morning dose. The placebo regimen will be visually matched tablets to be taken with the same schedule as the active treatment.

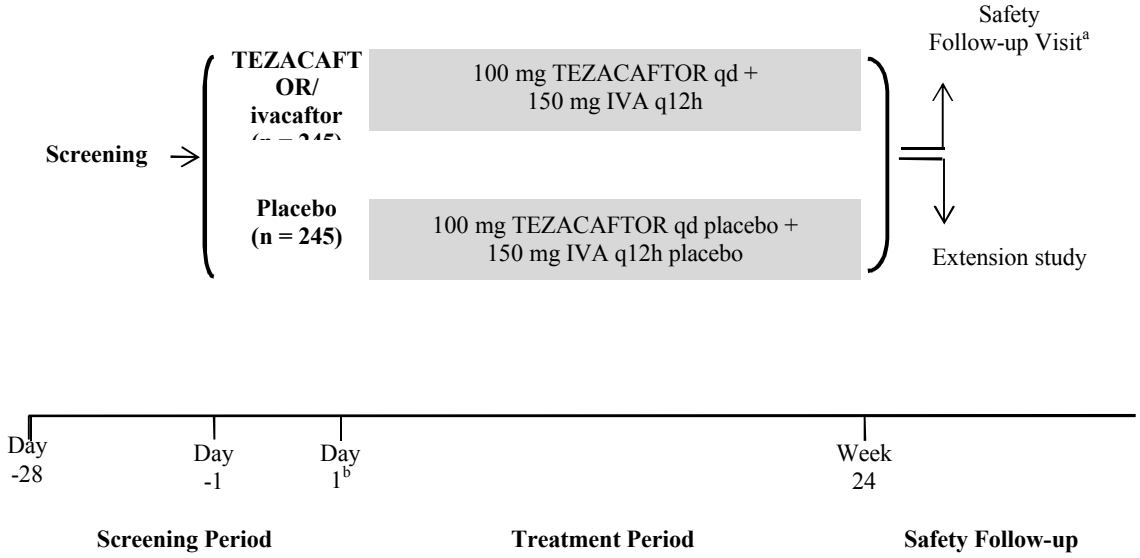
This study consists of a Screening Period, a Treatment Period, and a Safety Follow-up Visit. Approximately 490 subjects will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), sex (male versus female), and FEV_1 severity determined during the Screening Period (<70% versus ≥70% predicted) and then randomized (1:1) to either TEZ/IVA or placebo as shown in Figure 6-1.

Subjects who complete the Week 24 Visit will be offered the opportunity to enroll into the extension phase of Study 106, if they meet the relevant eligibility requirements.

All subjects will be required to complete study assessments for all scheduled visits, regardless of whether they have prematurely discontinued study drug treatment prior to Week 24 (see Protocol Section 8.1.4).

A schematic of the study design is shown in Figure 6-1.

Figure 6-1 Schematic of the Study Design



IVA: ivacaftor; q12h: every 12 hours; qd: once daily.

[a] The Safety Follow-up Visit is scheduled to occur 28 (±7) days after the Week 24 Visit. The Safety Follow-up Visit is not required for subjects who complete the Week 24 Visit in this study, and are eligible and enroll in an extension study of TEZACAFTOR in combination with ivacaftor.

[b] Approximately 490 subjects will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), sex (male versus female), and FEV_1 severity determined during the Screening Period (<70% versus ≥70% predicted) and randomized (1:1) before the first dose of study drug on Day 1.

6.2 Sample Size and Power

The study is powered for both the primary endpoint (change from baseline in ppFEV1) and a secondary endpoint of clinical interest (relative risk of pulmonary exacerbations).

The primary efficacy endpoint is the absolute change from baseline in percent predicted FEV_1 through Week 24.

The null hypothesis to be tested is that the mean absolute change from baseline in percent predicted FEV_1 through Week 24 is the same for TEZ/IVA and placebo. Assuming a common standard deviation (SD) of 8% in each arm, a sample size of 220 subjects in each treatment group will have at least 90% power to detect a treatment difference of 2.5% in percent predicted FEV_1 between treatment groups, using a 2-sided significance level of 0.05. If the above null hypothesis is rejected, the efficacy of TEZ/IVA will be considered established.

Power for pulmonary exacerbation:

Assuming the pulmonary exacerbation rate for placebo is 0.5 events in 24 weeks, with 220 subjects in each treatment group, the power to detect a 40% reduction in the pulmonary exacerbation rate in the active arm versus the placebo arm is about 92%. The power to detect a 33% reduction in the pulmonary exacerbation rate is about 78%.

This power calculation is based on an R simulation with 10,000 replications.

To adjust for a 10% dropout, a total sample size of 490 subjects is needed.

6.3 Randomization

Approximately 490 subjects (245 per arm) who meet eligibility criteria will be stratified by age at Screening Visit (<18 versus ≥18 years of age), sex (male versus female), and percent predicted FEV_1 severity determined during the Screening Period (<70 versus ≥70), and then randomized (1:1) to either TEZ/IVA or placebo. An interactive web response system (IWRS) will be used for randomization following a list of randomization codes generated by a designated vendor [redacted].

6.4 Blinding and Unblinding

This is a double-blind study.

6.4.1 Blinding

The subjects and all site personnel, including the investigator, the site monitor, and the study team, will be blinded with the exception of the following:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency. Such unblinding events will be fully documented (see below).
- Any site personnel for whom this information is important to ensure the safety of the subject and her fetus in the event of a pregnancy. Such unblinding events will be fully documented (see below).
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations
- Unblinded statistician preparing the final (production) randomization list who is not part of the study team
- Vertex Clinical Operations IWRS management
- Vertex Clinical Supply Chain
- IDMC
- Vendor preparing the unblinded analysis for the IDMC
- Vendor analyzing PK samples
- Vertex or vendor conducting the population PK analysis
- Vertex Medical Monitor may, for matters relating to safety concerns, unblind individual subjects at any time. Such unblinding events will be fully documented (see below).

Vertex Drug Metabolism and Pharmacokinetics laboratory personnel will not be involved in the conduct of the study and will be unblinded to the bioanalysis results and will remain blinded to subject number and treatment assignment.

Spirometry Data Blinding

Despite treatment blinding, knowledge of the spirometry results has the potential to suggest whether a subject has been administered active study drug or placebo. Therefore, during the conduct of the study, the Vertex study team will have no access to the post-dose spirometry data. The vendor for central reading of the spirometry data will only send the blinded spirometry files (blinded treatment group, with real values for screening and baseline, but with dummy values for all the spirometry assessment after baseline) to Vertex to be used for developing the statistical programs. Furthermore, subjects and their caregiver should not be informed of their study-related spirometry results during the Treatment Period regardless of whether the subject has prematurely discontinued treatment

Sweat Chloride Data Blinding

Despite treatment blinding, knowledge of the sweat chloride data has the potential to suggest whether a subject has been administered active study drug or placebo. Therefore, during the conduct of the study, the Vertex study team will have no access to the post-dose sweat chloride data; dummy data will be used to develop statistical programs. During the process of locking the clinical database, after all study visits have been completed, access to treatment-blinded sweat chloride data will be provided to a small group of individuals (a biostatistician, a statistical programmer, a validation statistical programmer, and a clinical reviewer) who are part of the Vertex study team. This small group will review the sweat chloride data to ensure there are no significant data issues and will use the blinded data set to refine the statistical programs.

6.4.2 Unblinding

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The unblinding method will be either a manual or electronic process.

Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators should use their best judgment as to whether to unblind without first attempting to contact the medical monitor to discuss and agree to the need for unblinding. If investigators deem that it is not necessary to unblind immediately, they will first attempt to contact the medical monitor to discuss and agree to the need for unblinding. If investigators have tried but are unable to reach the medical monitor, they should use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding.

Contact information for the medical monitor (or appropriate backup) will be provided in a separate document.

In addition, the Vertex Medical Information Call Center [redacted] will answer calls 24 hours a day, 7 days a week, 365 days of the year, and will triage these calls to the study medical monitor or appropriate backup.

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor should be notified within 24 hours of the unblinding event. The reason and the date of the unblinding will be documented clearly in the subject's study file. Information about the treatment assignment obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with sponsor (Vertex), contract research organization (CRO), or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS or designee, per Protocol Section13.1.2.

Vertex GPS or designee will also unblind any SAE reports in compliance with regulatory reporting requirements. In addition, the Vertex medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time.

7 ANALYSIS SETS

The following analysis sets are defined: All Subjects Set, Randomized Set, Full Analysis Set (FAS), and Safety Set.

The **All Subjects Set** is defined as all subjects who have been randomized or have received at least 1 dose of study medication. This analysis set will be used in subject listings and the disposition summary table, unless otherwise specified.

The **Randomized Set** is defined as all subjects who have been randomized.

The **Full Analysis Set** (FAS) is defined as all randomized subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug.

The **Safety Set** is defined as all subjects who received at least 1 dose of study drug.

8 STATISTICAL ANALYSIS

8.1 General Considerations

All individual subject data in the All Subject Set will be presented in data listings. The Schedule of Assessments is provided in Section 11.1. The precision standards are provided in Section 11.6.

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.

Baseline Value, unless otherwise specified, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to or on the first dose of study drug. For ECGs, the baseline will be defined as the average of the 3 pre-treatment measurements (triplicate) on Day 1. For sweat chloride, the baseline value will be the mean of last assessment values on the left and the right arm prior to the first dose of the study drug.

Change (Absolute Change) from baseline will be calculated as Post-baseline value − Baseline value.

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

Treatment Emergent (TE) Period will include the time from the first dose of study drug to the Safety Follow-up Visit, or to 28 days after the last dose of the study drug for subjects who do not have a Safety Follow-up Visit, or to the last participation date in the study (i.e., the day right before the first study dose in the extension study for subjects who enrolled into the extension study), whichever occurs first. The TE period will be used for safety analyses unless otherwise specified.

Unscheduled Visits: Unscheduled visit measurements will be included in the following:

1. derivations of measurements at scheduled visits per specified visit windowing rules below;
2. derivations of baseline/last on-treatment measurements;
3. derivations of the maximum/minimum on-treatment values and maximum/minimum changes from baseline values for safety analyses;
4. data listings where appropriate.

Visit Windowing Rules: Section 11.2 defines the windows for protocol-defined visits. The windows will be applied using the following rules for both scheduled and unscheduled visits:

1. If no measurement is available within a visit window, the assessment will be considered missing for the visit;
2. If there is more than one measurement available within the same visit window, use the following rules:

- For all efficacy parameters, if there are multiple measurements within a visit window, the record at the scheduled visit will be used. Otherwise,
    - The record closest to the target day will be used;
    - If there are multiple records with the same distance to the target day, the latest record will be used.
    - Assessments at early treatment termination (ETT) visit will follow the windowing rules for regular visits up to Week 24.
    - Assessments at safety follow-up (SFU) visit will follow the windowing rules for regular visits if they fall within the upper boundary of the window for

Week 24, or remain as SFU if they go beyond the upper boundary of the window for Week 24.

- For all safety parameters, if there are multiple measurements within a visit window, then 1) the record closest to the target day will be used; 2) if there are multiple records within the same distance from the target day, the latest record will be used; or 3) SFU visit will not be windowed; instead, it will be used according to the nominal visit in relevant analyses.

Note, spirometry assessments, BMI, weight, and height will be used for both efficacy and safety purposes. Their measurements will follow the visit windowing rules for efficacy parameters.

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.

8.2 Background Characteristics

8.2.1 Subject Disposition

In the summary table of subject disposition, the number of subjects in the following categories will be presented by treatment and overall:

- All Subjects Set (randomized or dosed)
- Randomized Set
- Full Analysis Set (FAS)
- Safety Set

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

- Completed treatment regimen
- Prematurely discontinued the treatment (any tablet) and the reason for discontinuations
- Completed study
- Prematurely discontinued the study and the reasons for discontinuations
- Rollover to extension

A listing will be provided for subjects who discontinued treatment or who discontinued from the study, along with reasons for discontinuations.

The number and percentage of randomized subjects will be summarized by stratification factor, and by country and by site, using the number of subjects being randomized to each treatment group as the denominator. A randomization listing will be provided with subjects ordered by randomization date.

8.2.2 Demographics and Baseline Characteristics

The following demographic data will be summarized by treatment and overall based on the FAS:

- Age at Screening
- Sex
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Geographic region (North America, Europe)

The following baseline characteristics will be summarized:

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

Stratification categories (in addition to sex) will also be summarized:

- Age groups at screening (< 18, ≥18 years)
- Percent predicted FEV_1 at screening (<70, ≥70)

Disease characteristics at baseline will include the following:

- Percent predicted FEV_1 categories(<40, ≥40- <70, ≥70-≤90, >90)
- Percent predicted FEV_1
- Sweat chloride
- CFQ-R Respiratory Symptoms domain
- FEV_1 (L)
- FVC (L)
- Percent predicted FVC
- $FEF_{25-75\%}$ (L/sec)
- Percent predicted $FEF_{25-75\%}$
- FEV_1/FVC

- Use of dornase alfa
- Use of inhaled antibiotic
- Use of azithromycin
- Use of bronchodilator
- Use of inhaled bronchodilator (short-acting only, [short-acting and long-acting] or long-acting only)
- Use of inhaled hypertonic saline
- Use of inhaled corticosteroids
- Colonization of *Pseudomonas aeruginosa* (Positive, Negative)

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 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 and preferred term. The corresponding data listing will also be provided.

In addition, the number of subjects reported to have had positive cultures for respiratory pathogens in the 2 years prior to screening (i.e., answered yes on the respiratory microbiology form) will be summarized by test and subcategories within the test. The corresponding data listing will be provided. Hospitalization and clinic visit history in the past year will be listed.

8.2.4 Prior and Concomitant Medications

Medications taken during this study will be coded using the World Health Organization Drug Dictionary Enhanced (WHO-DDE) and categorized as the following:

- **Prior medication:** any medication that started before the first dose of study drug, regardless of when the medication ended.
- **Concomitant medication:** medication continued or newly received at or after the first dose of study drug through the end of TE period.
- **Post-treatment medication:** medication continued or newly received after the TE period.

A given medication can be classified as a prior, a concomitant, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment. If a medication has a missing or partially missing start/end date and it cannot be determined whether it was taken before the first dose, concomitantly, or beyond the TE period, it will be considered as prior, concomitant, and post-treatment.

For the FAS, prior medications and concomitant medications will be summarized descriptively by: 1) preferred name; and 2) anatomic class (ATC) level 1, ATC level 2, and preferred name. Frequent (≥5% in any treatment group) prior medications and concomitant medications will be summarized descriptively by preferred name. Post-treatment medications will be listed by subject.

As an intermediate step for programming purposes, medications with missing or partially missing start dates will use 2000 to impute a missing year, January for a missing month, and 1 for a missing day. Medications with missing or partially missing stop dates will use 2050 to impute for a missing year, December for a missing month, and the last day of the month for a missing day. The logic to decide the category of a medication is presented in Table 8-1:

Table 8-1 Logic for Determining the Category of a Medication

	Medication end 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

8.2.5 Study Drug Exposure

Exposure summaries will be based on the FAS.

Duration of study drug exposure is defined as follows: last dose date – first dose date + 1 day, regardless of any interruption in dosing between the first and the last dose.

Duration of study drug exposure expressed in weeks will be summarized descriptively (number, mean, SD, median, minimum, and maximum) and also into the following categories: ≤2 weeks, >2- ≤4 weeks, >4 - ≤8 weeks, >8 - ≤16 weeks, and >16 - ≤24 weeks, >24 weeks. Additionally, the total duration of study drug exposure, defined as the sum of the subject's duration of treatment exposure and expressed in patient years, will be provided.

8.2.6 Study Drug Compliance

Study drug compliance will be measured by the compliance rate and be summarized based on the FAS.

Compliance rate will be calculated as follows:

100 × [1 - (Total number of days study drug interrupted) / (Duration of study drug exposure)].

The total number of days of study drug interrupted is defined as the sum of (number of unique days of study drug interrupted in each interruption interval), where number of days of study drug interrupted in each interval is defined as the interruption end date - the corresponding interruption start date + 1.

The Compliance rate will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max and into the categories of <80% or ≥80%.

A list of subjects with <80% of compliance rate will be provided.

8.2.7 Important Protocol Deviations

Important protocol deviations (IPD) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. IPDs rules will be developed and finalized before database lock.

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

- Subject entered the study despite violation of any inclusion or exclusion criteria
- Subject was less than 80% compliant with study medications
- Subject received excluded concomitant medications
- Subject received the wrong treatment or incorrect doses
- Subject remained in study despite meeting withdrawal criteria

Occurrence of any of these events should be considered as potential IPDs, but the blinded team should categorize them as IPDs only if they have the potential to affect interpretation of study results.

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

8.3 Efficacy Analysis

Unless otherwise defined, all efficacy analyses described in this section will be based on the FAS. The FAS will be used in the summary of demographics and baseline characteristics and analyses of the efficacy data; subjects will be analyzed according to their randomized treatment assignment.

8.3.1 Primary Efficacy Endpoint

8.3.1.1 Definition of Primary Efficacy Endpoint

The primary efficacy endpoint is the absolute change from baseline in percent predicted FEV_1 (with a unit of percentage points) through Week 24.

Percent predicted FEV_1 is the ratio of FEV_1 (L) to the predicted FEV_1 (L), expressed as a percentage. The predicted FEV_1 will be calculated using the Hankinson[1] and Wang[2] standards; details are in Section 11.3.

8.3.1.2 Primary Analysis of Primary Efficacy Endpoint

The primary analysis will be based on a mixed model for repeated measures (MMRM) implemented using SAS PROC MIXED with a REPEATED statement. The null hypothesis to be tested is that the mean absolute change from baseline in percent predicted FEV_1 through Week 24 is the same for TEZ/IVA and placebo. A *P* value of 0.05 or less will be interpreted as sufficient evidence to reject the null hypothesis.

The model includes absolute change from baseline in percent predicted FEV_1 at each post-baseline visit (Day 15, and Weeks 4, 8, 12, 16, and 24) as the dependent variables, and the following fixed effects: treatment, visit, treatment-by-visit interaction, sex, age group (<18 versus ≥18 years old) at Screening, baseline percent predicted FEV_1, and baseline percent predicted FEV_1-by-visit interaction. An unstructured covariance structure will be used to model the within-subject errors. If the analysis fails to converge, a compound symmetry covariance structure will be used. Denominator degrees of freedom for the *F*-test for fixed effects will be estimated using the Kenward-Roger approximation[3].

The LS Mean (SE) of the overall treatment difference between TEZ/IVA and placebo in absolute change from baseline in percent predicted FEV_1 from Day 15 through Week 24 will be presented along with the 95% confidence interval and a 2-sided *P* value.

Absolute change from baseline in percent predicted FEV_1 at each visit

The LS Mean (SE) of within-treatment group change from baseline at each post-baseline visit along with the 95% CI will be estimated from the above MMRM model. The LS Mean (SE) of the treatment difference between TEZ/IVA and placebo at each post-baseline visit will be provided along with the corresponding 95% CI and p-value. The LS means (with 95% CI) at each visit will also be plotted by treatment group. In addition, the post-baseline raw values and the absolute change from baseline in percent predicted FEV_1 at each post-baseline visit will be summarized descriptively (n, mean, SD, median, minimum, and maximum). The cumulative distribution of the absolute change from study baseline in $ppFEV_1$ through week 24 will be plotted by treatment group.

[redacted]

[redacted]

8.3.2 Secondary Efficacy Endpoints

The following are the key secondary efficacy endpoints:

- Relative change from baseline in percent predicted FEV_1 through Week 24
- Number of pulmonary exacerbations through Week 24
- Absolute change from baseline in BMI at Week 24
- Absolute change from baseline in CFQ-R respiratory domain through Week 24

The study also has the following other secondary efficacy endpoints:

- Time-to-first pulmonary exacerbation through Week 24
- Absolute change in sweat chloride from baseline through Week 24
- Absolute change in BMI z-score from baseline at Week 24 (in subjects <20 years of age at time of screening)
- Absolute change in body weight from baseline at Week 24

8.3.2.1 Definition of Secondary Efficacy Endpoints

8.3.2.1.1 Key Secondary Efficacy Endpoints

Relative change in percent predicted FEV_1 from baseline through Week 24

The calculations of percent predicted FEV_1 and the relative change from baseline at each post baseline visit will follow the definitions in Section 8.3.1.1and Section 8.1.

Number of pulmonary exacerbations through Week 24

The pulmonary exacerbation (PEx) analysis period will start from the first dose of study drug and end on the last efficacy assessment up to Week 24.

Pulmonary exacerbation: A pulmonary exacerbation 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 number of pulmonary exacerbations through Week 24 will be analyzed by comparing the *annualized number of pulmonary exacerbations* for each treatment group. It will be calculated as

$$48 \times (\text{total number of pulmonary exacerbations}) / (\text{total duration of post-baseline assessment in weeks}),$$

where total number of pulmonary exacerbations and total duration of post-baseline assessment are obtained from all subjects in the same treatment group.

Absolute change from baseline in BMI at Week 24

To calculate absolute change from baseline in BMI at Week 24, BMI will be calculated as:

$$\text{BMI} = \text{Weight (kg)}/(\text{height } [\text{m}^2])$$

Absolute change from baseline in CFQ-R respiratory domain through Week 24

The absolute change from baseline in the respiratory domain of the CFQ-R (Pooled 'Children Ages 12 and 13' Version and 'Adolescents and Adults' Version) through Week 24 will be analyzed based on the *CFQ-R scaled scores*, as elaborated below.

The CFQ-R[5,6,7] is a valid CF-specific instrument that measures quality-of-life domains. This study uses three different versions of CFQ-R forms in this study:

- CFQ-R for Children Ages 12 and 13 has a total of 35 questions to form 8 domains. All questions are scored 1, 2, 3, or 4.
- CFQ-R for Adolescents and Adult (subjects 14 years and older) has a total of 50 questions to form 12 domains. Question 43, which is scored 1, 2, 3, 4, or 5, is not used in calculating any domain; all the other 49 questions are scored 1, 2, 3, or 4.
- CFQ-R for Parents/Caregivers (subjects 13 years and younger) has a total of 44 questions to form 11 domains. Question 37, which is scored 1, 2, 3, 4, or 5, is not used in calculating any domains; all the other 43 questions are scored 1, 2, 3, or 4.

For all three CFQ-R versions, to calculate the score for each domain, the response scores on the negatively phrased questions are reversed (reversed scores = 5 – response scores) so that 1 always represents the worst condition and 4 always represents the best condition.

The scaled score for each domain ranges from 0 (worst condition) to 100 (best condition). It is calculated as follows:

Scaled score for a domain = 100 × (mean(scores of all questions in that domain) - 1)/3

The scaled score for a specific domain will not be calculated if more than half of the questions in the domain have missing scores.

Table 8-2, Table 8-3, and Table 8-4 provide the questions included in each domain, the questions with the reversed scores, as well as the maximum number of missing questions for the CFQ-R for Children Ages 12 and 13, the CFQ-R for Adolescents and Adults, and the CFQ-R for Parents/Caregivers respectively. The CFQ-R scoring manual is also provided in Section 11.4.

Table 8-2 CFQ-R for Children Ages 12 and 13

Domain	Questions		Reversed questions	Maximum number of missing questions
	Total	Individual		
Physical	6	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5	3
Emotion	8	7, 8, 9, 10, 11, 12, 13, 14	14	4
Social	7	20, 21, 22, 23, 24, 25, 26	20, 22, 24, 26	3
Body	3	27, 28, 29	-	1
Eat	3	15, 17, 19	19	1
Treatment burden	3	16, 18, 30	18	1
Respiration	4	31, 32, 33, 34	-	2
Digestion	1	35	-	0

Table 8-3 CFQ-R for Adolescents and Adults (Subjects 14 Years and Older)

Domain	Questions		Reversed questions	Maximum number of missing questions
	Total	Individual		
Physical	8	1, 2, 3, 4, 5, 13, 19, 20	13	4
Role	4	35, 36, 37, 38	35	2
Vitality	4	6, 9, 10, 11	6, 10	2
Emotion	5	7, 8, 12, 31, 33	-	2
Social	6	22, 23, 27, 28, 29, 30	23, 28, 30	3
Body	3	24, 25, 26	-	1
Eat	3	14, 21, 50	-	1
Treatment burden	3	15, 16, 17	15, 17	1
Health perceptions	3	18, 32, 34	18, 32, 34	1

Table 8-3 CFQ-R for Adolescents and Adults (Subjects 14 Years and Older)

Domain	Questions		Reversed questions	Maximum number of missing questions
	Total	Individual		
Weight	1	39	-	0
Respiration*	6	40, 41, 42, 44, 45, 46	43	3
Digestion	3	47, 48, 49	-	1

*: Question 43 not used to calculate a domain.

Table 8-4 CFQ-R for Parents/Caregivers (Subjects 13 Years and Younger)

Domain	Questions		Reversed questions	Maximum number of missing questions
	Total	Individual		
Physical	9	1, 2, 3, 4, 5, 13, 14, 15, 16	15	4
Vitality	5	8, 9, 10, 11, 12	10, 12	2
Emotion	5	6, 7, 23, 25, 26	6	2
School	3	27, 28, 29	28	1
Body	3	19, 20, 21	-	1
Eat	2	17, 44	-	0
Treatment burden	3	18, 30, 31	31	1
Health perceptions	3	22, 24, 32	22, 24, 32	1
Weight	1	33	-	0
Respiration*	6	34, 35, 36, 38, 39, 40	37	3
Digestion	3	41, 42, 43	-	1

*: Question 37 not used to calculate a domain.

8.3.2.1.2 Other Secondary Efficacy Endpoints

Time to First Pulmonary Exacerbation through Week 24

The *time to first pulmonary exacerbation* is defined as the number of days from the first dose of study drug to the date of the first pulmonary exacerbation.

Absolute change in sweat chloride from baseline through Week 24

Sweat chloride will be collected at baseline and 3 post-baseline time points (Weeks 4, 16, and 24). Values > 160 mmol/L or < 10 mmol/L will be set to missing.

Absolute change from baseline in sweat chloride will be calculated as, $mean(SW_{Left}, SW_{Right}) - SW_{Base}$, where SW_{Left} and SW_{Right} are the measurements obtained on the left and right arms, respectively, at a particular visit and SW_{base} is the mean of right and left baseline measurements. If one of the two measurements at a time point is missing, the other will be used as the mean.

Note: A volume of ≥15 µL is required for an accurate determination of sweat chloride. Any results reported as having volume <15 µL or "Quantity Not Sufficient" (QNS) will be considered missing.

Definition of Baseline: If sweat chloride collection was initiated for one arm prior to first dose and initiated for the other arm after the first dose, the baseline will consist of the single pre-dose measurement. If both sweat collections were initiated after the first dose, the baseline sweat chloride result will be considered missing for analysis purposes.

Absolute change from baseline in BMI z-score at Week 24 for subjects <20 years old at screening

BMI will be calculated from weight and height at baseline and at the 6 post-baseline time points (Day 15, Week 4, 8, 12, 16, and 24).

BMI, adjusted for age and sex, will be referred to as BMI-for-age z-score (BMI z-score). BMI z-score will be calculated by using Centers for Disease Control and Prevention (CDC) growth charts[8]. The BMI z-score will be calculated as follows:

$$z = \begin{cases} \dfrac{\left(\dfrac{X}{M}\right)^{L} - 1}{LS}, & L \neq 0 \\ \dfrac{\ln\left(\dfrac{X}{M}\right)}{S}, & L = 0 \end{cases}$$

where X is the derived BMI value in kg/m^2 based on the raw weight and raw height and L, M, and S are selected from the CDC BMI-for-age chart by subject sex and age. The BMIAGE file contains these parameters by sex (1=male, 2=female) and age; it is available at: http://www.cdc.gov/growthcharts/percentile_data_files.htm. SAS code for calculating percentiles and z-scores is available at: http://www.cdc.gov/growthcharts/computer_programs.htm.

NOTE: The CDC BMI-for-age charts are designed for use in pediatric populations (2 to 20 years of age); in this analysis plan, BMI z-score will be calculated only for subjects between 2 and <20 years of age at screening.

Absolute change from baseline in body weight at Week 24

Weight will be collected at baseline and at 6 post-baseline time points (Day 15, Week 4, 8, 12, 16, and 24) according to the Schedule of Assessments (see Section 11.1). The absolute change from baseline in body weight will be calculated at each post-baseline visit following the general definition of the change from baseline in Section 8.1.

8.3.2.2 Analysis of Secondary Efficacy Endpoints

8.3.2.2.1 Analysis of Key Secondary Efficacy Endpoints

Relative change from baseline in ppFEV$_1$ through Week 24

Analysis for the relative change from baseline in ppFEV$_1$ through Week 24 will be similar to that for the primary analysis. The LS Mean (SE) of the overall treatment difference between TEZ/IVA and placebo in the relative change from baseline in percent predicted FEV$_1$ from Day 15 through Week 24 will be presented along with the 95% confidence interval and a 2-sided *P* value.

The LS Mean (SE) of within-treatment group relative change from baseline at each post-baseline visit along with the corresponding 95% CI and p-value will be estimated from the same MMRM model. The LS Mean (SE) of the treatment difference between TEZ/IVA and placebo at each post-baseline visit will be provided along with the corresponding 95% CI and p-value. The LS means (with 95% CI) at each post-baseline visit will also be plotted by treatment group. Summary statistics of raw values and absolute change from baseline in ppFEV$_1$ at each visit will be presented. The cumulative distribution of the average relative change from study baseline in ppFEV$_1$ through week 24 will be plotted by treatment group.

Number of pulmonary exacerbations through Week 24

A negative binomial generalized linear model will be used to compare the rates of pulmonary exacerbations over the 24-week treatment period for the two treatment groups. The estimated rate ratio and the associated 95% CI and p-value will be provided. In this model, the dependent variable will be the number of pulmonary exacerbations through Week 24, (including both on treatment events and events after treatment discontinuation). Treatment, sex, age group at screening (<18 vs. ≥ 18 years old), and baseline percent predicted FEV$_1$ will be included as covariates. The log of time spent in the study will be treated as the offset in this model. A log link function will be used in this model. If the model does not converge, the negative binomial regression model will be replaced with a Poisson regression model with the same covariates, offset variable, and link function.

Absolute change in BMI from baseline at Week 24

Analysis of the absolute change from baseline in BMI at Week 24 will be based on an MMRM model similar to that used for the primary analysis, with baseline ppFEV$_1$ replaced by baseline BMI, and baseline ppFEV$_1$-by-visit interaction replaced by baseline BMI-by-visit interaction. The treatment difference in terms of BMI at Week 24 will be estimated from this model, along with the 95% CI and the associated p-value.

The LS Mean (SE) of within-treatment group absolute change from baseline in BMI at each of the other post-baseline visits along with the corresponding 95% CI and p-value will be estimated from the same MMRM model. The LS Mean (SE) of the treatment difference between TEZ/IVA and placebo at the other post-baseline visit will be provided along with the corresponding 95% CI and p-value. The LS means (with 95% CI) at each post-baseline visit will also be plotted by treatment group. Summary statistics for the raw values and the absolute change from baseline in BMI at each visit will be presented. The cumulative

distribution of the absolute change from study baseline in BMI at week 24 will be plotted by treatment group.

Absolute change from baseline in CFQ-R respiratory domain through Week 24

Analysis for the absolute change from baseline in CFQ-R respiratory domain (Pooled 'Children Ages 12 and 13' Version and 'Adolescents and Adults' Version) through Week 24 will be similar to that used for the primary analysis, with baseline $ppFEV_1$ replaced by baseline in CFQ-R respiratory domain, and baseline $ppFEV_1$-by-visit interaction replaced by CFQ-R respiratory domain baseline-by-visit interaction. The LS Mean (SE) of the overall treatment difference between TEZ/IVA and placebo in CFQ-R respiratory domain from Day 15 through Week 24 will be presented along with the 95% confidence interval and a 2-sided *P* value.

The LS Mean (SE) of within-treatment group absolute change from baseline at each post-baseline visit along with the corresponding 95% CI and p-value will be estimated from the same MMRM model. The LS Mean (SE) of the treatment difference between TEZ/IVA and placebo at each post-baseline visit also will be provided along with the corresponding 95% CI and p-value. The LS means (with 95% CI) at each post-baseline visit also will be plotted by treatment group. Summary statistics for the raw values and the absolute change from baseline in CFQ-R respiratory domain at each visit will be presented. The cumulative distribution of the average relative change from study baseline in CFQ-R respiratory domain through week 24 will be plotted by treatment group.

8.3.2.2.2 Multiplicity adjustment

A hierarchical testing procedure will be used to control the overall Type I error for the multiple endpoints tested at $\alpha = 0.05$. For a test at any step to be considered statistically significant within the testing hierarchy, the test must be statistically significant at the 0.05 level, and all previous tests (if any) within the hierarchy must also be statistically significant. The testing hierarchy is as follows:

1. Absolute change from baseline in $ppFEV_1$ through Week 24
2. Relative change from baseline in $ppFEV_1$ through Week 24
3. Number of pulmonary exacerbations through Week 24
4. Absolute change in BMI from baseline at Week 24
5. Absolute change in CFQ-R respiratory domain score from baseline through Week 24

8.3.2.2.3 Analysis of Other Secondary Efficacy Endpoints

Time to first pulmonary exacerbation through Week 24

Analyses for the time to first pulmonary exacerbation through Week 24 will be based on a Cox regression model that will include treatment, sex, age group at screening (<18 vs. ≥18 years old), and baseline $ppFEV_1$ as covariates. In addition, the Kaplan-Meier (KM) method

will be used to estimate the cumulative exacerbation-free rate; the associated plot will be provided.

Subjects without any protocol-defined pulmonary exacerbation event by or prior to Week 24 will be considered censored at the date of the last visit (up to Week 24).

Note: If in either treatment group fewer than 5 subjects have pulmonary exacerbations, the Cox regression will not be performed and analysis of time-to-first event will be restricted to the Kaplan-Meier estimates.

Absolute change in sweat chloride from baseline through Week 24

Analysis of this variable will be performed using a model analogous to that used for the primary endpoint, with baseline $ppFEV_1$ replaced by baseline sweat chloride value, and baseline $ppFEV_1$-by-visit interaction replaced by baseline sweat chloride value-by-visit interaction. The LS Mean (SE) of the overall treatment difference between TEZ/IVA and placebo in absolute change from baseline in sweat chloride from Day 15 through Week 24 will be presented along with the 95% confidence interval and a 2-sided *P* value.

The LS Mean (SE) of within-treatment group absolute change from baseline at each post-baseline visit along with the corresponding 95% CI and p-value will be estimated from the same MMRM model. The LS Mean (SE) of the treatment difference between TEZ/IVA and placebo at each post-baseline visit also will be provided along with the corresponding 95% CI and p-value. The LS means (with 95% CI) at each post-baseline visit also will be plotted by treatment group. Summary statistics for the raw values and the absolute change from baseline in sweat chloride at each visit will be presented.

Absolute change in BMI z-score from baseline at Week 24 for subjects <20 years old at screening

Analysis for BMI z-score will be based on an MMRM model similar to that used for the analysis of the absolute change from baseline in BMI at Week 24, with baseline BMI replaced by baseline BMI z-score, and baseline BMI-by-visit interaction replaced by baseline BMI z-score-by-visit interaction. The LS Mean (SE) of the treatment difference between TEZ/IVA and placebo in absolute change from baseline in BMI z-score at Week 24 will be presented along with the 95% confidence interval and a 2-sided *P* value.

The LS Mean (SE) of within-treatment group absolute change from baseline at each of the other post-baseline visits along with the corresponding 95% CI and p-value will be estimated from the same MMRM model. The LS Mean (SE) of the treatment difference between TEZ/IVA and placebo at each post-baseline visit also will be provided along with the corresponding 95% CI and p-value. The LS means (with 95% CI) at each post-baseline visit also will be plotted by treatment group. Summary statistics for the raw values and the absolute change from baseline in BMI z-score at each visit will be presented.

Absolute change in body weight from baseline at Week 24

Analysis of body weight will be based on an MMRM model similar to that used for the analysis of the absolute change from baseline in BMI at Week 24 with baseline BMI replaced by baseline body weight, and baseline BMI-by-visit interaction replaced by baseline body

weight-by-visit interaction. The LS Mean (SE) of the treatment difference between TEZ/IVA and placebo in absolute change from baseline in body weight at Week 24 will be presented along with the 95% confidence interval and a 2-sided *P* value.

The LS Mean (SE) of within-treatment group absolute change from baseline at each of the other post-baseline visits along with the corresponding 95% CI and p-value will be estimated from the same MMRM model. The LS Mean (SE) of the treatment difference between TEZ/IVA and placebo at each post-baseline visit also will be provided along with the corresponding 95% CI and p-value. The LS means (with 95% CI) at each post-baseline visit also will be plotted by treatment group. Summary statistics for the raw values and the absolute change from baseline in weight at each visit will be presented.

Absolute change from baseline in percent predicted FEV_1 through Week 24 using on-treatment measurements only

This analysis will be similar to that used for the primary analysis of the primary efficacy endpoint. The key difference is that this MMRM will include only the measurements up to the date of the last dose for subjects in the FAS. This analysis will use assessments taken between the first dose date through 5 days after the last dose of study drug.

Absolute change from baseline in percent predicted FEV1 at Week 24 using ANCOVA model

For the absolute change from baseline in percent predicted FEV_1 at Week 24, an ANCOVA model, including treatment, sex, age group (<18 vs. ≥18 years old) at screening, and baseline percent predicted FEV_1 will be used to assess the treatment difference in the absolute change from baseline in percent predicted FEV_1 at Week 24. Missing percent predicted FEV1 data will not be imputed. The LS Mean (SE) of the treatment difference between TEZ/IVA and placebo in absolute change from baseline in percent predicted FEV_1 at Week 24 will be presented along with the associated 95% confidence interval and a 2-sided *P* value.

[redacted]

[redacted]

8.4 Safety Analysis

All safety analyses will be based on the Safety Set. Subjects will be analyzed according to the treatment they actually received if they took the same study drug during the entire study period. For subjects receiving study drug from more than one treatment group by error, the treatment group allocation will be TEZ/IVA.

The overall safety profile of study drug will be assessed in terms of the following safety and tolerability endpoints:

- Adverse events
- Clinical laboratory values (hematology, serum chemistry, coagulation studies, vitamin levels, lipid panel, and urinalysis)
- Standard 12-lead electrocardiograms
- Vital signs
- Pulse oximetry
- Postdose ppFEV$_1$ and FEV$_1$ (L) and change from predose.

Safety endpoints will be analyzed using data during the treatment emergent period. Only descriptive summaries will be presented and no statistical testing is planned.

Treatment Emergent (TE) Period will include the time from the first dose of study drug to the Safety Follow-up Visit, or to 28 days after the last dose of the study drug for subjects who do not have a Safety Follow-up Visit, or to the last study participation day (i.e., the day right before the first study dose in the extension study for subjects who enrolled into the extension study), whichever occurs first.

For the purpose of safety analyses, the entire study period will then be further divided into 3 segments:

- The **pre-treatment period** is the period after the informed consent/assent date and before the start date of the TE period.
- The **treatment-emergent period** (TE period) is defined as above.
- The **post-treatment period** is the period after the end of the TE period to the date of the last study record in the clinical database.

8.4.1 Adverse Events

For analysis purposes, AEs will be categorized as pretreatment AEs, treatment-emergent adverse events (TEAEs), or post-treatment AEs:

- **Pretreatment AE:** any AE that started before the first dose of study drug.
- **TEAE:** any AE that increased in severity or that was newly developed at or after the first dose of study drug through the end of TE period.
- **Post-treatment AE:** any AE that increased in severity or that was newly developed after the TE period.

For AEs with a missing or partial start date, if there is no clear evidence that the AEs started (or increased in severity) before or after the first dose date, the start date will be imputed to be the first dose date and the AE will be considered to be a TEAE (see Section 11.7). Similarly, if there is no clear evidence that the AEs started (or increased in severity) before or after the start of the post-treatment period, the start date will be imputed to be the earliest possible time in the TEAE period and the AE will be considered to be a TEAE. As an intermediate step for programming purposes, imputation rules for missing or partially missing AE start/end dates are defined in Section 10.7.

Based on the reported severity and relationship to study drugs, TEAEs can be categorized as follows:

By relationship to the study drugs, treatment emergent adverse events (TEAEs) will be classified into the 4 categories:

- Not related
- Unlikely related
- Possibly related
- Related.

By severity, TEAEs will be classified into the 4 categories:

- **Mild (Grade 1):** Mild level of discomfort and does not interfere with regular activities
- **Moderate (Grade 2):** Moderate level of discomfort and significantly interferes with regular activities
- **Severe (Grade 3):** Significant level of discomfort and prevents regular activities
- **Life-threatening (Grade 4 and 5):** Any adverse drug experience that places the subject, in the view of the investigator, at immediate risk of death.

8.4.1.1 Overview of Pre-treatment AEs and Treatment Emergent AEs

An overview of the pre-treatment AEs will be summarized in the following categories:

- Any pre-treatment AEs
- Grade 3/4 pre-treatment AEs
- Pre-treatment SAEs by severity.

An overview of all TEAEs will be summarized in the following categories:

- Any TEAEs
- Grade 3/4 TEAEs
- TEAEs by relationship
- TEAEs by severity
- TEAEs leading to treatment discontinuation (this category will capture TEAEs leading to discontinuation of either the morning or the evening tablets)
- TEAEs leading to treatment interruption (this category will capture TEAEs leading to interruption of either the morning or the evening tablets)
- TE SAE by severity
- TEAE leading to death

8.4.1.2 TEAEs and TE SAEs by System Organ Class (SOC) and Preferred Term (PT)

The number and percentage of subjects with TEAEs will be summarized by treatment group, MedDRA system organ class (SOC), and preferred term (PT), where multiple occurrences of the same AE for the same subject will be counted only once. The summary table will be presented in descending order of frequencies in the TEZ/IVA treatment group. TE SAEs will be summarized similarly.

8.4.1.3 TEAEs and TE SAEs by Preferred Term (PT)

The number and percentage of subjects with TEAEs will be summarized by treatment group and PT, where multiple occurrences of the same AE for the same subject will be counted

only once. The summary table will be presented in descending order of frequencies in the TEZ/IVA treatment group. TE SAEs will be summarized similarly.

8.4.1.4 TEAEs and TE SAEs by SOC, PT, and Relationship

The number and percentage of subjects with TEAEs will be summarized by treatment group, SOC, PT, and relationship, where multiple occurrences of the same AE for the same subject will be counted only once according to the worst relationship to study drug. The summary table will be presented in descending order of frequencies in the TEZ/IVA treatment group. TE SAE will be summarized similarly.

8.4.1.5 TEAEs and TE SAEs by SOC, PT, and Severity

The number and percentage of subjects with TEAEs will be summarized by treatment group, SOC, PT, and severity, where multiple occurrences of the same AE for the same subject will be counted only once according to the worst severity. The summary table will be presented in descending order of frequencies in the TEZ/IVA treatment group. TE SAE will be summarized similarly.

8.4.1.6 Respiratory Events and Symptoms

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

- Chest discomfort
- Dyspnoea
- Respiration abnormal

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

- Asthma
- Bronchial hyperreactivity
- Bronchospasm
- Wheezing

A summary of respiratory symptoms and events will be presented by preferred term.

8.4.1.7 Elevated Transaminase

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

- Alanine aminotransferase abnormal
- Alanine aminotransferase increased
- Aspartate aminotransferase abnormal

- Aspartate aminotransferase increased
- Transaminases abnormal
- Transaminases increased
- Liver function test abnormal
- Liver function test increased
- Hypertransaminasaemia
- Hepatic enzyme abnormal
- Hepatic enzyme increased.

A summary of elevated transaminase will be presented by preferred term.

8.4.1.8 Summaries of Respiratory Events and Elevated Transaminase by Treatment Interval

Respiratory events and elevated transaminase also will be summarized by the following treatment intervals:

0-1 Weeks: [Day1, Day7]

>1 -2 Weeks: [Day8, Day14]

>2 -8 Weeks: [Day15, Day56]

>8-16 Weeks: [Day57, Day112]

>16 -24 Weeks: [Day113, Day168]

>24 Weeks: [Day169, end of TE period])

8.4.1.9 Subgroup Analysis

TEAEs will be summarized by SOC and PT for the following subgroups:

- Age at screening (<18, ≥18 years)
- Percent predicted FEV_1 at baseline (<40, ≥40-<70, ≥70)
- Sex
- Region (North America, Europe)

Separate listings will be presented for TEAEs leading to treatment discontinuation, TE SAEs, and all deaths.

For all AEs, the CRF captures the action taken for VX661/IVA pills separately from the AE action taken for IVA monotherapy pills. As a result, it is possible that, in the final database (after DBL), the AE actions taken for the two agents (fixed dose 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.

8.4.2 Clinical Laboratory Values

For treatment emergent laboratory measurements, the raw values and change from baseline values for the continuous hematology, chemistry and coagulation results will be summarized in SI units by treatment group at each scheduled time point. For hematology, chemistry and coagulation, the number and percentage of subjects with an abnormal low (<LLN) value and with an abnormal high (>ULN) value at each scheduled time point will be summarized.

The number and percentage of subjects with hematology, chemistry and coagulation values meeting the defined threshold criterion will be summarized by treatment, lab parameters, and visit. The threshold criteria are provided in Section 11.5, Table 11-6 and Table 11-7.

For all LFT results (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], direct bilirubin, total bilirubin, and gamma-glutamyl transferase [GGT]), the following additional analyses will be conducted:

- A listing of subjects with elevated LFT results during the TE period will be presented. For each subject in the listing, LFT assessments at all visits will be included.
- For each of the LFTs, mean values (±SD) will be plotted by visit, and a box plot of the LFT value/ULN will be plotted by visit.
- The incidence of LFTs meeting threshold criteria against the baseline threshold criteria also will be summarized by treatment group, LFT parameters, and visit (only shifts to values worse than baseline will be presented).
- A scatter plot of the maximum ALT value across visits versus the maximum total bilirubin value also will be presented. The ALT and total bilirubin values will be presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3xULN for ALT and a horizontal line corresponding to 2xULN for total bilirubin. A similar graph of maximum AST value versus maximum total bilirubin value will be presented as well.

A summary table for the shift from baseline to the value at Week 24 will be presented by treatment group for vitamin levels and lipid panel. A box plot of vitamin levels and lipid panel also will be plotted against visit.

In addition, a listing containing individual subject hematology, chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points. Subjects with positive pregnancy test results will be listed. Abnormal urinalysis results also will be listed by treatment and subject.

8.4.3 Standard 12-Lead Electrocardiogram

For treatment-emergent ECG measurements, a summary of raw values and change from period baseline values will be provided by treatment group at each scheduled time point for the following standard 12-lead ECG measurements: PR, QTc for HR intervals (QTcF), QRS

duration, and HR. In addition, the mean value at each time point will be plotted by treatment group for QTcF and heart rate.

The number and percentage of subjects with ECG events meeting threshold criteria during the treatment-emergent period will be summarized by treatment, ECG parameters, and visit. The threshold criteria are provided in Section 11.5, Table 11-8.

8.4.4 Vital Signs

For treatment emergent vital signs measurements, the raw values and changes from baseline will be summarized by treatment group at each scheduled time point for systolic and diastolic blood pressure (mmHg), body temperature (^{o}C), HR (beats per minute), and respiratory rate (breaths per minute). In addition, the mean value at each time point will be plotted by treatment group for systolic and diastolic blood pressure.

The number and percentage of subjects with vital signs meeting threshold criteria during the treatment-emergent period will be summarized by treatment, vital signs parameters, and visit. The threshold criteria are provided in Section 11.5, Table 11-9.

8.4.5 Pulse Oximetry

A summary of raw values and change from baseline values will be provided by treatment group at each scheduled time point for the percent of oxygen saturation by pulse oximetry. In addition, the mean value at each visit will be plotted 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 treatment-emergent period will be tabulated by treatment groups.

8.4.6 Postdose Spirometry

For subjects < 18 years old at screening, a summary of the raw values and change from predose value for percent predicted FEV_1 will be provided by treatment group at each time point (2-hour and 4-hour postdose) on Day 1 and Day 15 In addition, a box plot by study day and treatment group will be provided for each time point.

The above analyses will be repeated for FEV_1 [in L]

In addition, the number and percentage of subjects with percent predicted FEV_1 decline ≥10, ≥15, and ≥20 percentage points in the absolute change from the predose value will be summarized by treatment arm and by assessment day and time. The number and percentage of subjects with ≥0.20 L decrease from baseline in FEV_1 will be summarized by treatment arm and by assessment day and time.

8.4.7 Physical Examination

PE findings will be presented in a data listing only.

8.4.8 Ophthalmology Examination

Ophthalmologic findings (cataracts) during the treatment-emergent period will be summarized by treatment group. The numbers and percentages of subjects with cataract at screening will be presented. The numbers and percentages of subjects with cataract after the first dose of study drug will be presented. In addition, ophthalmology examination results will be provided in a data listing for subjects who have developed any cataracts during the treatment-emergent period. Subjects with cataract at screening will also be listed.

8.5 Safety Supportive Endpoints

8.5.1 Spirometry

The following summaries regarding the decline in pre-dose spirometry measurements will be provided.

- The number and percentage of subjects with ≥10, ≥15, and ≥20 percentage points decrease from baseline in percent predicted FEV_1 at each post-baseline visit.
- The number and percentage of subjects with ≥0.20 L decrease from baseline in FEV_1 at each post-baseline visit.

Subjects with ≥10 percentage points decrease from baseline in $ppFEV_1$ or ≥0.20 L decrease from baseline in FEV_1 will be listed. The listing will include raw values and absolute/relative changes from period baseline in $ppFEV_1$ and FEV_1 at each time point.

8.5.2 Weight and BMI

The following summaries will be provided, based on the post-baseline measurements through Week 24:

- The number and percentage of subjects with ≥3.0 kg decrease, and ≥6.0 kg decrease, in absolute change from baseline in weight will be summarized at all visits.
- The number and percentage of subjects with ≥1.5 decrease, and ≥3.0 decrease, in absolute change from baseline in BMI will be summarized at all visits.

Subjects with ≥3.0 kg decrease in absolute change from baseline in Weight or ≥1.5 decrease in the absolute change from baseline in BMI will be listed. The listing will include the average raw values and absolute changes from baseline in weight and BMI at all visits.

[redacted]

[redacted]

9 INTERIM AND DMC ANALYSES

9.1 Interim Analysis

No formal interim analysis is planned.

9.2 DMC Analysis

An independent data monitoring committee (IDMC) was formed before study initiation. The IDMC's objectives and operational details were defined in a separate document (IDMC Charter) which was finalized before the first subject was screened in the study. The IDMC conducted regular planned safety reviews of study data as outlined in the IDMC Charter and IDMC Analysis Plan.

10 REFERENCES

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11 APPENDICES

11.1 Schedule of Assessments

Table 11-1 Screening Period Assessments – Study VX14-661-106

Event/Assessment	Screening Period (Day -28 through Day -1)
Informed consent and assent (when applicable)	X
Demographics	X
Medical history	X
Ophthalmological history	X
CFQ-R[a]	X
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CF genotype[b]	X
FSH[c]	X
Serum pregnancy test (all females of childbearing potential)[d]	X
Hematology	X
Coagulation	X
Serum chemistry	X
Urinalysis	X
Weight and height[e]	X
Ophthalmologic examination[f]	X
Complete PE	X
Vital signs[g]	X
Pulse oximetry[g]	X
Standard 12-lead ECG[h]	X
Spirometry[i]	X
[redacted]	[redacted]
Inclusion/exclusion criteria review	X
Prior and concomitant medications	X
Sweat chloride	X

[a] The CFQ-R, [redacted] must be completed before the start of any other assessments scheduled for that visit.

[b] All subjects will be tested for CF genotype. Specific instructions will be provided in the Laboratory Manual.

[c] FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be ≥40 mIU/mL to be considered postmenopausal.

[d] Any female subject who does not meet the criteria for non-childbearing potential is considered to be of childbearing potential and must have a serum pregnancy test.

[e] Weight and height will be measured with shoes off.

[f] An ophthalmologic examination will be conducted on subjects of all ages by an ophthalmologist. The ophthalmologic examination does not need to be repeated if there is documentation of an examination that met the protocol criteria and that was conducted within 3 months before the Screening Period (Protocol Section 11.7.8). Subjects with clinically significant cataracts, lens opacity, Y-suture, or lamellar rings will be excluded.

[g] Vital signs and pulse oximetry will be collected after the subject has been at rest (seated or supine) for 5 minutes.

[h] A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes.

[i] Spirometry may be performed pre- or post-bronchodilator (Protocol Section 11.6.1).

[j] [redacted]

Table 11-1 Screening Period Assessments – Study VX14-661-106

Event/Assessment	Screening Period (Day -28 through Day -1)
AEs and SAEs	**Continuous from signing of the ICF and assent (where applicable) through the Safety Follow-up Visit**

AE: adverse event; CF: cystic fibrosis; CFQ-R: CF Questionnaire–Revised; [redacted]; ECG: electrocardiogram; FSH: follicle-stimulating hormone; ICF: informed consent form; PE: physical examination; [redacted] SAE: serious adverse event; [redacted]; US: United States.

Table 11-2 Treatment Period and Safety Follow up Visit Assessments – VX14-661-106

Event/Assessment[k]	Day 1	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit[l]	Safety Follow-up Visit 28 (± 7) days After the last dose of study drug (if applicable)[m]
Clinic visit	X	X	X	X	X	X	X[n]	X	X	X
Telephone contact							X[o]			
Inclusion and exclusion criteria review	X									
CFQ-R[p]	X		X	X	X	X		X	X	X
[redacted]										
[redacted]										
[redacted]										
[redacted]										
Weight and height[r]	X	X	X	X	X	X		X	X	X

[k] All assessments will be performed before dosing unless noted otherwise. If study drug is not administered on the day of the visit (i.e., study drug interruption or premature discontinuation of study drug treatment), only 1 set of assessments will be collected. Subjects who discontinue treatment early will continue to complete all other scheduled study visits for assessments of efficacy (spirometry, CFQ-R, sweat chloride, height, and weight), [redacted], and other events related to outcome (hospitalizations, pulmonary exacerbations, etc.) as detailed in Protocol Section 8.1.4.

[l] If the subject prematurely discontinues study treatment, an Early Treatment Termination (ETT) Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (± 7) days after their last dose of study drug. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required. See Protocol Section 8.1.4.

[m] A Safety Follow-Up Visit is not required for subjects who complete the Week 24 Visit and have enrolled in a separate extension study of TEZACAFTOR in combination with ivacaftor within 28 days after the last dose of study drug.

[n] Females of childbearing potential will have a clinic visit for a urine pregnancy test. This clinic visit is not required for females who are **not** of childbearing potential or males.

[o] Telephone contact will be made for female subjects not of childbearing potential and males to assess the subject's status, any AEs, concomitant medications, treatments, and procedures.

[p] All questionnaires must be completed before the start of any other assessments scheduled at that visit. The CFQ-R must be completed first, followed by the [redacted] (Protocol Section 8.1.4)Subjects will need to complete a CFQ-R, [redacted] at the Early Treatment Termination Visit (Protocol Section 8.1.4).

[redacted]

[r] Weight and height will be measured before dosing with shoes off. Height will be collected only for subjects 21 years of age or younger.

Table 11-2 Treatment Period and Safety Follow up Visit Assessments – VX14-661-106

Event/Assessment[k]	Day 1	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit[l]	Safety Follow-up Visit 28 (± 7) days After the last dose of study drug (if applicable)[m]
Ophthalmologic exam								X [s]	X [t]	X [j]
Complete PE[u]	X							X	X	
Pregnancy test[v]	urine		urine	urine	urine	urine	urine	serum	serum	serum
Standard 12-lead ECG[w]	X	X	X	X	X	X		X	X	X
Vital signs[x]	X	X	X	X	X	X		X	X	X
Pulse oximetry[n]	X	X	X	X	X	X		X	X	X
Spirometry[y]	X	X	X	X	X	X		X	X	X
Sweat chloride[z]	X		X			X		X	X	
Urinalysis	X							X	X	X
Hematology	X	X	X	X	X	X		X	X	X

[s] All subjects will have an ophthalmologic examination conducted by a licensed ophthalmologist at Week 24. This exam may be completed within 4 weeks before the Week 24 Visit, but must be completed by the end of the Week 24 Visit. Subjects <18 years of age at the Screening Visit who complete an ophthalmologic exam at the ETT Visit will not be required to complete another ophthalmologic exam at the Week 24 Visit.

[t] Subjects <18 years of age at the Screening Visit who discontinue treatment after receiving at least 1 dose of study drug treatment, and subjects <18 years of age at the screening who complete treatment but do not enroll in a separate extension study of VX-661/ivacaftor within 28 days of the last dose of study drug will have an ophthalmologic exam conducted by a licensed ophthalmologist at the Safety Follow-up Visit or ETT Visit (see Protocol Section 11.7.8). The exam may be completed at either the ETT or Safety Follow-up Visit, but must be completed by the date of the Safety Follow-up Visit. Subjects who complete an ophthalmologic exam at the ETT Visit or Week 24 Visit will not be required to complete another ophthalmologic exam at a subsequent visit.

[u] Subjects will have a complete physical examination (as defined in Protocol Section 11.7.3) as noted. Symptom-targeted physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

[v] Pregnancy tests will be performed for all female subjects of childbearing potential. A urine β-hCG test will be performed on Day 1 (before first dose of study drug) and every 4 weeks thereafter.

[w] All standard 12-lead ECGs will be performed before dosing and after the subject has been supine for at least 5 minutes. At the Days 1 and 15 Visits, ECGs will be collected before dosing and at 1.5, 3, 4, and 6 hours after the morning dose; the 4-hour postdose ECG will be collected before the 4-hour postdose spirometry assessment. ECGs collected on Day 1 before dosing will be performed in triplicate. If study drug is not administered on the day of the visit (i.e., because of study drug interruption or permanent discontinuation of study drug), only 1 ECG will be collected.

[x] Vital signs and pulse oximetry will be collected before dosing and after the subject has been at rest (seated or supine) for at least 5 minutes.

[y] At all visits, spirometry will be performed for all subjects prebronchodilator and before dosing (Protocol Section 11.6.1) At Day 1 and Day 15, subjects <18 years of age at the Screening Visit will have additional spirometry performed at 2 and 4 hours postdose. If more than 1 spirometry assessment is required at a visit, bronchodilators should be withheld until the last scheduled spirometry assessment is completed.

[z] Sweat chloride collection will occur approximately 1 hour before the PK sample collection and before the morning dose of the study drugs. At each time point, 2 samples will be collected, 1 from each arm (left and right). Collection of sweat chloride will not overlap with any other study assessments.

Table 11-2 Treatment Period and Safety Follow up Visit Assessments – VX14-661-106

Event/Assessment[k]	Day 1	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit[l]	Safety Follow-up Visit 28 (± 7) days After the last dose of study drug (if applicable)[m]
Coagulation	X							X	X	X
Serum chemistry	X[aa]	X	X	X	X	X		X	X	X
Lipid panel[bb]	X				X			X	X	
Vitamin levels	X				X			X	X	
PK sampling[cc]	X				X	X			X	X
[redacted]		[redacted]								
[redacted]	[redacted]							[redacted]		
[redacted]	[redacted]							[redacted]		[redacted]
[redacted]	[redacted]							[redacted]		
[redacted]	[redacted]							[redacted]		
Other events related to outcome[ee]	X	X	X	X	X	X	X	X	X	
Randomization[ff]	X									
Meal(s) or snack(s) at site[gg]	X	X	X	X	X	X				
Study drug dosing[hh]	**Day 1 through Week 24**									
Study drug count		X	X	X	X	X		X	X	

aa Blood samples will be collected before the first dose of study drug.

bb Blood samples will be collected for the lipid panel following at least a 4-hour fast.

cc PK samples will be collected on Day 1 at predose; at Week 12 (predose, 0.5, 3, and 6 hours after the morning dose); and at Week 16 (predose, 2, 4, and 8 hours after the morning dose). At the Safety Follow-up Visit and ETT Visit, a single blood sample for PK will be collected. If study drug is not administered on the visits of Weeks 12 and 16 (i.e., study drug interruption or permanent discontinuation of study drug), only 1 PK blood sample will be collected at each of these 2 visits.

[redacted]

ee Other events related to outcome include assessments relating to pulmonary exacerbations, administration of antibiotic therapy for sinopulmonary signs or symptoms, and hospitalizations (Protocol Section 11.6.12).

ff Randomization must occur after all inclusion and exclusion criteria are met and before the first dose of study drug. Randomization will be done through IWRS. Randomization may occur on Day -1.

gg Fat-containing food such as a standard "CF" high-fat, high-calorie meal or snack will be provided at the site to subjects after all predose assessments have occurred.

hh The study drug should be administered every 12 hours (± 2 hours) within 30 minutes of starting a meal with fat-containing food such as a standard "CF" high-fat, high-calorie meal or snack. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. The final dose of study drug will be administered the evening before the Week 24 Visit.

Table 11-2 Treatment Period and Safety Follow up Visit Assessments – VX14-661-106

Event/Assessment[k]	Day 1	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit[l]	Safety Follow-up Visit 28 (± 7) days After the last dose of study drug (if applicable)[m]
Concomitant medications[ii]	X	X	X	X	X	X	X	X	X	X
Concomitant treatments and procedures	X	X	X	X	X	X	X	X	X	X
AEs and SAEs[jj]	**Continuous from signing of the ICF and Assent (where applicable) through the Safety Follow-up Visit**									

AE: adverse event; β-hCG: beta-human chorionic gonadotropin; CF: cystic fibrosis; CFQ-R: CF Questionnaire–Revised; [redacted] ECG: electrocardiogram; ETT: Early Treatment Termination; IWRS: interactive web response system; PE: physical examination; PK: pharmacokinetic; [redacted]; SAE: serious adverse event; [redacted]

[ii] All concomitant medications are collected through the Safety Follow-up Visit for all subjects. For subjects who discontinue treatment and are followed for certain efficacy assessments after the ETT Visit (see Protocol Section 8.1.4), concomitant antibiotic therapy for 'sinopulmonary signs and symptoms' are collected through the Week 24 Visit, as described in Protocol Section 11.6.12.1.

[jj] SAEs that occur after the Safety Follow-Up Visit and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours** as described in Protocol Section 13.1.2.2.

11.2 Analysis Visit Window Mapping Rules for Efficacy and Safety Measurements

Table 11-3 Visit Window Mapping Rules

Assessments	Visit	Target Study Day	Visit Window (in study days)
• Weight and height • Vital signs • Pulse oximetry • Labs ○ Chemistry ○ Hematology	Baseline	1	[screening visit, pre-dose Day 1]
	Day 15	15	[1*, 22]
	Week 4	29	[23,43]
	Week 8	57	[44, 71]
	Week 12	85	[72, 99]
	Week 16	113	[100, 141]
	Week 24	169	[142, 183]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up Visit (SFU)	N/A	Efficacy assessments: follow the individual visit window to be mapped to individual visits if measured before / on Day 183 or remain as SFU if otherwise. Safety assessments: remain as SFU.
• Spirometry • Standard 12-lead ECG	Baseline	1	[screening visit, pre-dose Day 1]
	Day 1 Predose and Postdose (Spirometry, or ECG)	1	Nominal
	Day 15 Predose and Postdose (Spirometry, or ECG)	15	Nominal
	Day 15 Spirometry, or ECG	15	[2,15] if no nominal Day 15
	Week 4 (Spirometry, or ECG)	29	[Nominal Day 15+1, 43] if there is nominal Day 15; [16, 43] otherwise.
	Week 8	57	[44, 71]
	Week 12	85	[72, 99]
	Week 16	113	[100, 141]

	Week 24	169	[142, 183]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up Visit (SFU)	N/A	Efficacy assessments: follow the individual visit window to be mapped to individual visits if measured before / on Day 183 or remain as SFU if otherwise. Safety assessments: remain as SFU.
• CFQ-R	Baseline	1	[screening visit, Day 1]
	Week 4	29	[2, 43]
	Week 8	57	[44, 71]
	Week 12	85	[72, 99]
	Week 16	113	[100, 141]
	Week 24	169	[142, 183]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
• Sweat chloride	Baseline	1	[screening visit, pre-dose Day 1]
	Week 4	29	[1*, 71]
	Week 16	113	[72, 141]
	Week 24	169	[142, 183]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
• Vitamin levels • Lipid panel	Baseline	1	[screening visit, pre-dose Day 1]
	Week 12	85	[1*, 127]
	Week 24	169	[128, 183]

• Complete PE • [redacted] • Labs ○ Coagulation ○ Urinalysis	Baseline	1	[screening visit, pre-dose Day 1]
	Week 24	169	[1*, 183]
	Safety Follow-up Visit (no Complete PE, [redacted])	N/A	Nominal

1* only include day 1 post-dose measurements.

Note:

1. To apply the above visit windows, please first determine the baseline measurements based on the first dose of study medication and then label Day 1 for the date of the first dose of study drug, and use the nominal visit names to label SFU (for safety).

2. After baseline, and SFU (for safety) measurements are determined; the above visit windows will be applied to determine the analysis visit names for all remaining measures at scheduled or unscheduled visits.

3. For spirometry and ECG assessments on day 1 and Day 15, no visit windowing rule shall be applied. Instead, nominal visits will be used.

4. For all efficacy parameters, if there are multiple measurements within a visit window, the record at the scheduled visit will be used.

    - If there are no measurements at the scheduled visit, then the record closest to the target day will be used;

    - If there are multiple records with the same distance to the target day, the latest record will be used.

5. For all safety parameters, if there are multiple measurements within a visit window, then 1) the record closest to the target day will be used; or 2) if there are multiple records within the same distance from the target day, the latest record will be used.

6. Spirometry, BMI, Weight and Height are following the efficacy windowing rules.

<u>Special handling for ECG:</u>

- On Day 1 & Day 15, ECGs will be collected before dosing and at 1.5, 3, 4, and 6 hours after the morning dose. None of the measures on Day 1 or Day 15 will be mapped into other visits.
    - On Day 1, if there are assessments for triplicate prior to the first dose, the average of the triplicate will be used as the baseline. Only the pre-dose assessments of the triplicate will be used for the baseline. If all the measurements for triplets are missing or post-dose, the last non-missing pre-dose assessment will be used as the baseline.
    - Day 1 post-dose and Day 15 pre-/post-dose measurements will be analyzed based on nominal visit names.
- After the analysis visit names for Day 15 measurements are assigned, measures within the window [study day of Day 15 visit, 43] will be mapped to Week 4 as appropriate for safety analysis (following rules in Section 8.1)
- For other post-dose visits, the visit window in the above table will apply.

11.3 Coefficients for Hankinson and Wang Methods for Calculating Predicted Spirometry Parameters

Percent predicted FEV_1 is the ratio of FEV_1 (L) to the predicted FEV_1 (L), expressed as a percentage. The predicted FEV_1 (L) will be calculated using the Hankinson[1] and Wang[2] standards.

The Hankinson standard will be applied to male subjects 18 years and older and female subjects 16 years and older; the Wang standard will be applied to male subjects 6 to 17 years and female subjects 6 to 15 years of age. During the study, the subjects who have a birthday that would move them from Wang to Hankinson will use the Wang standard before that birthday and the Hankinson standard at or after that birthday.

Hankinson Normal Values (HNVs) will be calculated for FEV_1, forced vital capacity (FVC), forced expiratory flow mid expiratory phase ($FEF_{25-75\%}$), and FEV_1/FVC% using the Hankinson equation:

$$\text{Predicted lung function parameter} = b0+b1 \times age+b2 \times age^2+ b3 \times height^2$$

In the equation, height is given in centimeters, age is given in years, and the coefficients b_0, b_1, b_2, and b_3 are determined based on subject's sex, race, and age group as shown in Table 11-3.

Wang Normal Values (WNVs) will be calculated for FEV_1, FVC, $FEF_{25-75\%}$, and FEV_1/FVC using the Wang equation:

$$\ln(\text{Predicted lung function parameter}) = \alpha + \beta \ln(\text{height})$$

Wang Normal Values (WNVs) will be calculated for FEV_1, FVC, $FEF_{25-75\%}$, and FEV_1/FVC using the Wang equation. In the equation, height is given in meters, and the coefficients α and β are determined based on subject's sex, race, and age as shown in **Table 11-4** and Table 11-5.

If either height or age is missing, and the spirometry measurement is non-missing, the last non-missing value of height and age will be used in the calculation of predicted values.

Table 11-3 HNVs Equation Coefficients by Sex, Race, and Age

Parameter	Sex	Race	Age (years)	b_0	b_1	b_2	b_3
HNV_{FEV1}	Male	Caucasian	<20	-0.7453	-0.04106	0.004477	0.00014098
			≥20	0.5536	-0.01303	-0.000172	0.00014098
		African American	<20	-0.7048	-0.05711	0.004316	0.00013194
			≥20	0.3411	-0.02309		0.00013194
		Mexican American	<20	-0.8218	-0.04248	0.004291	0.00015104
			≥20	0.6306	-0.02928		0.00015104
	Female	Caucasian	<18	-0.8710	0.06537		0.00011496
			≥18	0.4333	-0.00361	-0.000194	0.00011496
		African American	<18	-0.9630	0.05799		0.00010846
			≥18	0.3433	-0.01283	-0.000097	0.00010846
		Mexican American	<18	-0.9641	0.06490		0.00012154
			≥18	0.4529	-0.01178	-0.000113	0.00012154
HNV_{FVC}	Male	Caucasian	<20	-0.2584	-0.20415	0.010133	0.00018642
			≥20	-0.1933	0.00064	-0.000269	0.00018642
		African American	<20	-0.4971	-0.15497	0.007701	0.00016643
			≥20	-0.1517	-0.01821		0.00016643
		Mexican American	<20	-0.7571	-0.09520	0.006619	0.00017823
			≥20	0.2376	-0.00891	-0.000182	0.00017823
	Female	Caucasian	<18	-1.2082	0.05916		0.00014815
			≥18	-0.3560	0.01870	-0.000382	0.00014815
		African American	<18	-0.6166	-0.04687	0.003602	0.00013606
			≥18	-0.3039	0.00536	-0.000265	0.00013606
		Mexican American	<18	-1.2507	0.07501		0.00014246
			≥18	0.1210	0.00307	-0.000237	0.00014246
$HNV_{FEF25-75\%}$	Male	Caucasian	<20	-1.0863	0.13939		0.00010345
			≥20	2.7006	-0.04995		0.00010345
		African American	<20	-1.1627	0.12314		0.00010461
			≥20	2.1477	-0.04238		0.00010461
		Mexican American	<20	-1.3592	0.10529		0.00014473
			≥20	1.7503	-0.05018		0.00014473
	Female	Caucasian	<18	-2.5284	0.52490	-0.015309	0.00006982
			≥18	2.3670	-0.01904	-0.000200	0.00006982

		African American	<18	-2.5379	0.43755	-0.012154	0.00008572
			≥18	2.0828	-0.03793		0.00008572
		Mexican American	<18	-2.1825	0.42451	-0.012415	0.00009610
			≥18	1.7456	-0.01195	-0.000291	0.00009610
$HNV_{FEV1/FVC\%}$	Male	Caucasian		88.066	-0.2066		
		African American		89.239	-0.1828		
		Mexican American		90.024	-0.2186		
	Female	Caucasian		90.809	-0.2125		
		African American		91.655	-0.2039		
		Mexican American		92.360	-0.2248		

Source: Reference 1. (Tables 4, 5 and 6)

Table 11-4 WNVs Equation Coefficients by Sex and Age in White Boys and Girls

		FEV_1		FVC		$FEF_{25-75\%}$		FEV_1/FVC	
Sex	**Age**	**α**	**β**	**α**	**β**	**α**	**β**	**α**	**β**
Male	6	-0.109	2.252	-0.024	2.470			-0.078	-0.248
	7	-0.104	2.270	-0.018	2.489			-0.086	-0.220
	8	-0.089	2.257	0.005	2.443	0.264	1.505	-0.091	-0.199
	9	-0.063	2.197	0.017	2.426	0.308	1.443	-0.086	-0.206
	10	-0.057	2.212	0.030	2.407	0.290	1.557	-0.081	-0.209
	11	-0.093	2.324	0.009	2.468	0.242	1.738	-0.101	-0.147
	12	-0.161	2.512	-0.061	2.649	0.165	1.982	-0.101	-0.133
	13	-0.292	2.843	-0.175	2.924	0.007	2.396	-0.116	-0.085
	14	-0.329	2.983	-0.219	3.060	0.014	2.483	-0.106	-0.087
	15	-0.141	2.709	-0.079	2.859	0.241	2.163	-0.060	-0.155

	16	0.062	2.409	0.104	2.591	0.503	1.764	-0.045	-0.178
	17	0.262	2.099	0.253	2.374	0.762	1.368	0.008	-0.272
Female	6	-0.109	1.949	-0.013	2.007			-0.097	-0.055
	7	-0.144	2.243	-0.062	2.385			-0.084	-0.132
	8	-0.137	2.239	-0.055	2.381	0.247	1.668	-0.079	-0.152
	9	-0.123	2.222	-0.039	2.351	0.254	1.710	-0.084	-0.128
	10	-0.161	2.364	-0.068	2.458	0.195	1.933	-0.092	-0.097
	11	-0.223	2.558	-0.120	2.617	0.161	2.091	-0.102	-0.061
	12	-0.264	2.709	-0.174	2.776	0.185	2.120	-0.090	-0.067
	13	-0.153	2.535	-0.061	2.576	0.294	1.976	-0.093	-0.040
	14	0.046	2.178	0.139	2.208	0.450	1.711	-0.096	-0.026
	15	0.148	2.008	0.210	2.099	0.581	1.486	-0.062	-0.093

Source: Reference 2. (Tables 2 and 3)

Table 11-5 WNVs Equation Coefficients by Sex and Age in Black Boys and Girls

		FEV_1		FVC		$FEF_{25-75\%}$		FEV_1/FVC	
Sex	**Age**	**α**	**β**	**α**	**β**	**α**	**β**	**α**	**β**
Male	6	-0.166	1.723	-0.088	1.961			-0.091	-0.152
	7	-0.122	1.846	-0.040	2.040			-0.091	-0.153
	8	-0.225	2.271	-0.094	2.323	0.097	1.544	-0.118	-0.104
	9	-0.142	2.059	-0.074	2.308	0.255	1.248	-0.079	-0.218
	10	-0.157	2.117	-0.110	2.417	0.230	1.428	-0.047	-0.303
	11	-0.176	2.166	-0.138	2.453	0.256	1.438	-0.048	-0.263
	12	-0.307	2.548	-0.224	2.710	0.085	1.936	-0.084	-0.162
	13	-0.486	2.962	-0.342	2.975	-0.121	2.476	-0.141	-0.018
	14	-0.472	3.010	-0.337	3.035	-0.115	2.536	-0.123	-0.050
	15	-0.318	2.789	-0.226	2.889	0.170	2.120	-0.070	-0.140
	16	0.074	2.140	0.058	2.425	0.663	1.299	0.018	-0.289
	17	0.053	2.223	0.148	2.310	0.505	1.618	-0.095	-0.087
Female	6	-0.288	2.182	-0.172	2.117			-0.109	0.059
	7	-0.250	2.158	-0.135	2.132			-0.104	-0.030
	8	-0.276	2.295	-0.176	2.362	-0.283	2.990	-0.103	-0.066
	9	-0.294	2.330	-0.200	2.452	0.025	2.062	-0.097	-0.104
	10	-0.344	2.507	-0.230	2.571	0.051	2.028	-0.120	-0.043
	11	-0.308	2.460	-0.204	2.526	0.078	2.006	-0.089	-0.105
	12	-0.219	2.312	-0.107	2.342	0.225	1.804	-0.115	-0.021
	13	-0.117	2.196	-0.042	2.294	0.418	1.504	-0.051	-0.148
	14	0.041	1.920	0.105	2.021	0.574	1.257	-0.063	-0.103
	15	0.203	1.662	0.253	1.787	0.599	1.281	-0.043	-0.139

Source: Reference 2. (Tables 4 and 5)

11.5 Threshold Analysis Criteria

Table 11-6 Threshold Criteria for Clinical Chemistry and Hematology

Parameter	Threshold Criteria	Comments
Clinical Chemistry		
CPK	>ULN - ≤ 2.5 x ULN >2.5 - ≤ 5 x ULN >5 - ≤ 10x ULN >10 x ULN	CTCAE grades 1-4
Creatinine	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	CTCAE grades 1-4
Blood Urea Nitrogen	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	Same criteria as creatinine No CTCAE
Sodium	Hyponatremia <LLN - ≥130 mmol/L <130 – ≥120 mmol/L <120 mmol/L	CTCAE grade 1, 3, 4 (No CTCAE grade 2)
	Hypernatremia >ULN - ≤ 150 mmol/L >150 mmol/L- ≤155 mmol/L >155 mmol/L - ≤ 160 mmol/L >160 mmol/L	CTCAE grade 1-4
Potassium	Hypokalemia <LLN – ≥ 3.0 mmol/L <3.0 – ≥ 2.5 mmol/L <2.5 mmol/L	CTCAE grade 1&2, 3, 4 (Grade 1 and 2 are the same)
	Hyperkalemia >ULN – ≤ 5.5 mmol/L >5.5 – ≤ 6.0 mmol/L >6.0 – ≤ 7.0 mmol/L >7.0 mmol/L	CTCAE grade 1-4

Total Cholesterol	>ULN – ≤ 7.75 mmol/L >7.75 – ≤ 10.34 mmol/L >10.34 – ≤ 12.92 mmol/L >12.92 mmol/L	CTCAE grade 1-4
Triglycerides	>1.71 – ≤ 3.42 mmol/L >3.42 – ≤ 5.7 mmol/L >5.7 – ≤ 11.4 mmol/L >11.4 mmol/L	CTCAE grade 1-4
Glucose	Hypoglycemia <3.0 – ≥ 2.2 mmol/L <2.2 - ≥ 1.7 mmol/L <1.7 mmol/L	CTCAE grade 1-4
	Hyperglycemia >ULN - ≤ 8.9 mmol/L >8.9 – ≤ 13.9 mmol/L >13.9 – ≤ 27.8 mmol/L >27.8 mmol/L	CTCAE grade 1-4
Albumin	<35 - ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4
Lipase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4
Direct bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	Same Criteria as Total Bilirubin No CTCAE Not in DILI Guidance
GGT	>ULN - ≤ 2.5 x ULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	CTCAE grade 1-4
Calcium	Hypercalcemia	CTCAE grade 1-4

	>ULN - ≤ 2.9 mmol/L >2.9 – ≤ 3.1 mmol/L >3.1 – ≤ 3.4 mmol/L >3.4 mmol/L	
	Hypocalcemia <LLN - ≥ 2.0 mmol/L <2.0 – ≥1.75 mmol/L <1.75 – ≥ 1.5 mmol/L <1.5 mmol/L	CTCAE grade 1-4
Magnesium	Hypermagnesemia >ULN - ≤ 1.23 mmol/L >1.23 – ≤ 3.30 mmol/L >3.30 mmol/L	CTCAE grade 1, 3, 4 No CTCAE grade 2
	Hypomagnesemia <LLN - ≥ 0.5 mmol/L <0.5 – ≥ 0.4 mmol/L <0.4 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
Inorganic phosphate	Hypophosphatemia <0.74 – ≥ 0.6mmol/L <0.6 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
ALT	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN >5 – ≤ 8 xULN >8 – ≤ 20.0 xULN >20.0 x ULN	Per FDA DILI Guidance Jul 2009 and CTCAE
AST	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN >5 – ≤ 8 xULN >8 – ≤ 20.0 xULN >20.0 x ULN	FDA DILI Guidance and CTCAE
ALT or AST	(ALT>ULN and ALT ≤ 3 xULN) or (AST>ULN and AST≤ 3 xULN) (ALT>3 xULN and ALT ≤ 5 xULN) or	FDA DILI Guidance

	(AST>3xULN and AST≤ 5 xULN) (ALT>5 xULN and ALT ≤ 8 xULN) or (AST>5xULN and AST≤ 8 xULN) (ALT>8 xULN and ALT ≤ 20 xULN) or (AST>8xULN and AST≤ 20 xULN) ALT>20 xULN or AST> 20 xULN	
Alkaline Phosphatase	>ULN - ≤ 1.5xULN >1.5 – ≤ 2.5 xULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	FDA DILI Guidance and CTCAE
Total Bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	FDA DILI Guidance and CTCAE
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
Hematology		
WBC	WBC decreased <LLN - ≥ 3.0 x 10e9 /L <3.0 – ≥ 2.0 x 10e9 /L <2.0 – ≥ 1.0 x 10e9 /L <1.0 x 10e9 /L	CTCAE grade 1-4
	Leukocytosis >100 x 10e9 /L	CTCAE grade 3 (only Grade available)
Lymphocytes	Lymphocyte decreased <LLN - ≥ 0.8 x10e9 /L <0.8 – ≥ 0.5 x10e9 /L <0.5 – ≥ 0.2 x10e9 /L <0.2 x10e9 /L	CTCAE grade 1-4
	Lymphocyte increased >4 – ≤ 20 x10e9/L >20 x10e9/L	CTCAE grade 2, 3 (only Grades available)

Neutrophils	Neutrophil decreased <LLN - ≥ 1.5 x10e9 /L <1.5 – ≥ 1.0 x10e9 /L <1.0 – ≥ 0.5 x10e9 /L <0.5 x10e9 /L	CTCAE grade 1-4
Hemoglobin	Hgb decreased (anemia) <LLN - ≥ 100 g/L <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 11-7 Threshold Criteria for Coagulation

Parameter	Threshold	Comments
Activated partial thromboplastin time (PTT)	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN	CTCAE grade 1-3

Table 11-8 Threshold Criteria for ECGs

Parameter	Threshold	Comments
HR	Bradycardia	Per HV grade 2, 3, plus shift change
	<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	
	Tachycardia	Per HV grade 1, 2, 3, plus shift change
	>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	
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 ms (Male)	
	>470 ms (Female)	
	≥500 ms	
	Increase from baseline >10 ms	
	Increase from baseline >20 ms	
	Increase from baseline >40 ms	
	Increase from baseline >60 ms	

Table 11-9 Threshold Criteria for Vital Signs

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

DBP	DBP increased >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	809/770 analyses
	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

11.6 Standards for Efficacy and Safety Variable Display in TFLs

Table 11-10 Precision Standards for Efficacy Variables

Variable Statistics	Number of Decimal Places
$ppFEV_1$ (%, absolute or relative change)	
Mean, LS mean, 95% CI	1
FEV_1 (L, absolute or relative change)	
FEF, FVC	
Mean, LS mean, 95% CI	2
CFQ-R	
Mean, LS mean, 95% CI	1
Sweat chloride (mmol/L)	
Mean, LS mean, 95% CI	1
BMI (kg/m^2)	
Mean	2
LS mean, 95% CI	2
BMI-for-age z-score	
Mean, LS mean, 95% CI	2
Weight (kg)	
Mean	1
LS mean, 95% CI	1
Weight-for-age z-score	
Mean, LS mean, 95% CI	2
Time-to-first clinical event of interest, e.g., pulmonary exacerbation	
Proportion of event-free, 95% CI	3
Hazard ratio (HR), 95% CI for HR	2

Normalized days with pulmonary exacerbations	
Mean	
	1
Number of events	0
Event rate	2

Number of decimal places for standard error and standard deviation will be the same as for the corresponding mean.

Table 11-11 Standard Display Units in Percent Predicted FEV1

Variable	Unit	Displayed Unit
$ppFEV_1$	percent	N/A
Absolute change in $ppFEV_1$	percent	Percentage points
Relative change in $ppFEV_1$	percent	%

11.7 Imputation Rules for Missing AE Start Date

For missing or partial AE start date, use the imputation rules below.

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

If the full (or partial) AE end date is NOT prior to the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date; otherwise, impute the AE start day as 1.

Otherwise, impute the AE start day as 1.

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

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

If the full (or partial) AE end date is NOT prior to the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date; otherwise, impute the AE start Month as January and the Day as 1.

Otherwise, impute the AE start Month as January and the Day as 1.

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

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site with no imputation. Also compare the full (or partial) AE end date to the first dose date. If the AE end date is prior to the first dose date then the AE should be considered as a pre-treatment AE. Otherwise, the AE will be considered as TEAE.