VERTEX

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX14-661-108, Version 3.0

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Efficacy and Safety of Ivacaftor and VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the F508del-CFTR Mutation, and a Second Allele With a CFTR Mutation Predicted to Have Residual Function

Author of SAP: [redacted]

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Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210, USA

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3 INTRODUCTION

This SAP, which describes the planned final analyses for the Study VX14-661-108 data, is based on the following:

- approved clinical study protocol (Version 3.0, dated 10 June 2016),
- approved electronic case report form (eCRF) (Version 3.0, dated 14 January 2016).

Study VX14-661-108 is a Phase 3, randomized, double-blind, placebo-controlled, 2-period, 3-treatment, crossover, multicenter study in subjects aged 12 years and older with CF, heterozygous for the F508del-CFTR mutation, and a second allele with a CFTR mutation predicted to have residual function. The study is designed to evaluate (i) the efficacy and safety of tezacaftor (TEZ; VX-661) in combination with ivacaftor (IVA; VX-770) and (ii) the efficacy and safety of IVA monotherapy in this patient population using an incomplete block design.

This SAP (Methods) documents the planned final statistical analyses of efficacy and safety endpoints defined in the study protocol for VX14-661-108, and describes the corresponding data presentations. It also documents analyses for additional efficacy and safety variables not specified in the protocol, which will provide supportive information to enhance the scientific understanding of the drug entity.

The study will also evaluate the pharmacokinetic (PK) characteristics of TEZ, IVA, and their metabolites in this patient population. PK analyses will be documented separately in the clinical pharmacology analysis plan (CPAP) for the study.

In addition, some exploratory endpoints were also described in the study protocol. Analysis of some of these endpoints is described in this SAP. Additional analyses of exploratory endpoints will be outside of the scope of this SAP and 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 database lock and treatment unblinding for the study and if the methods in this SAP differ from the methods described in the protocol, the SAP prevails.

4 STUDY OBJECTIVES

4.1 Primary Objective

To evaluate the efficacy of TEZ/IVA and IVA monotherapy through 8 weeks of treatment in subjects with CF who are heterozygous for the F508del mutation on the CFTR gene and a second allele with a CFTR mutation predicted to have residual function.

4.2 Secondary Objectives

- To evaluate the safety of TEZ/IVA through 8 weeks of treatment
- To evaluate the safety of IVA monotherapy through 8 weeks of treatment
- To investigate the pharmacokinetics (PK) of TEZ and its metabolite M1 (M1-TEZ), and IVA and its metabolite M1 (M1-IVA)

5 STUDY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoint

Absolute change in $ppFEV_1$ from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period.

5.1.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoint is:

- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period

The following are other secondary efficacy endpoints:

- Relative change in $ppFEV_1$ from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period
- Absolute change in sweat chloride from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period

5.2 Safety Endpoints

Safety and tolerability are secondary endpoints which will be evaluated based on assessments of:

- Adverse events (AEs)
- Clinical laboratory values (hematology, serum chemistry, coagulation studies, vitamin levels, lipid panel, and urinalysis)
- Standard digital 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 TEZ, M1-TEZ, IVA, and M1-IVA

6 STUDY DESIGN

6.1 Overview of Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, 2-period, 3-treatment, crossover, multicenter study in subjects aged 12 years and older with CF, heterozygous for the F508del-CFTR mutation, and a second allele with a CFTR mutation predicted to have residual function. A summary of mutations predicted to have residual function is in Section 10.8. This study is designed to evaluate (i) the efficacy and safety of TEZ/IVA and (ii) the efficacy and safety of IVA monotherapy in this patient population using an incomplete block design.

The treatment regimens are:

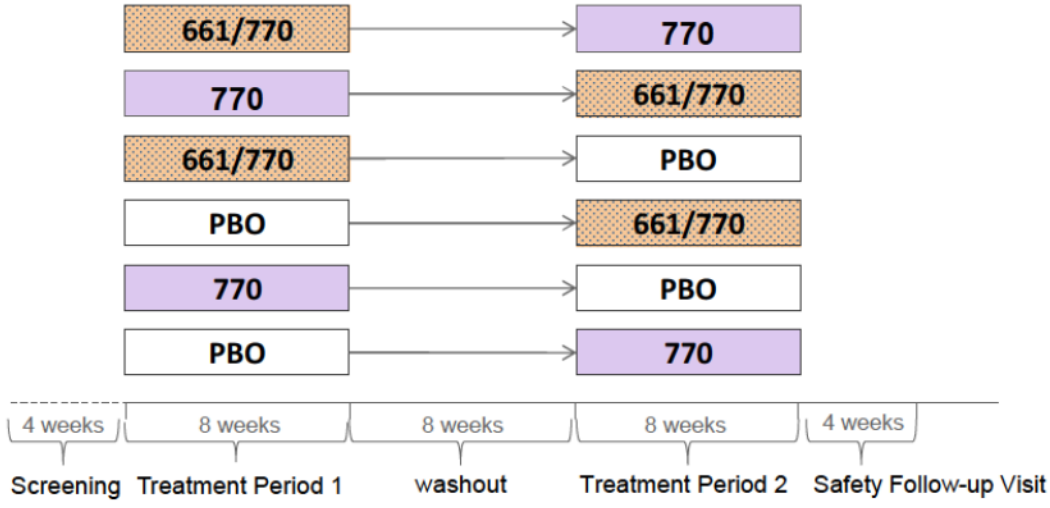
- TEZ/IVA combination treatment
    - Morning dose: 1 tablet fixed-dose combination of TEZ 100 mg/IVA 150 mg and 1 tablet IVA placebo
    - Evening dose: 1 tablet IVA 150 mg
- IVA monotherapy
    - Morning dose: 1 tablet placebo visually matched to the fixed-dose combination tablet and 1 tablet IVA 150 mg
    - Evening dose: 1 tablet IVA 150 mg
- Placebo
    - Morning dose: 1 tablet placebo visually matched to the fixed-dose combination tablet and 1 tablet placebo visually matched to IVA 150 mg
    - Evening dose: 1 tablet placebo visually matched to IVA 150 mg

This study includes a Screening Period (approximately 28 days), Treatment Period 1 (8 weeks), Washout Period (8 weeks), Treatment Period 2 (8 weeks), and Safety Follow-up Visit (approximately 28 days). Approximately 204 subjects (34 per sequence) will be enrolled and stratified by age at the Screening Visit (<18 versus ≥18 years of age), FEV_1 severity (determined during the Screening Visit; <70% versus ≥70% predicted), and type of residual function mutation on the second CFTR allele (Class V non-canonical splice mutation versus Classes II to IV residual function mutation; see Section 10.8), and then randomized (1:1:1:1:1:1) to 1 of the 6 treatment sequences, as shown in Figure 6-1. A minimum of 25% of enrolled subjects will carry a Class II to IV mutation on the second CFTR allele. Stratification of enrollment will be managed through the interactive web response system (IWRS). Enrollment into the non-canonical splice strata will be limited to no more than 75% of total enrollment.

- Sequence 1: TEZ/IVA in Treatment Period 1→washout→IVA monotherapy in Treatment Period 2
- Sequence 2: IVA monotherapy in Treatment Period 1→washout→TEZ/IVA in Treatment Period 2
- Sequence 3: TEZ/IVA in Treatment Period 1→washout→placebo in Treatment Period 2
- Sequence 4: placebo in Treatment Period 1→washout→TEZ/IVA in Treatment Period 2
- Sequence 5: IVA monotherapy in Treatment Period 1→washout→ placebo in Treatment Period 2
- Sequence 6: placebo in Treatment Period 1→washout→IVA monotherapy in Treatment Period 2

Subjects who complete the Week 24 Visit will be offered the opportunity to enroll in an extension study, if they meet the eligibility criteria for the extension study.

Figure 6-1 Schematic of the Study Design



661/770: TEZ/IVA; 770: IVA; PBO: placebo.

Subjects who prematurely discontinue study drug treatment will continue to complete all other scheduled study visits for assessment of efficacy through the end of the Treatment Period in which discontinuation occurred.

6.2 Sample Size and Power

The primary efficacy endpoint is the absolute change in $ppFEV_1$ from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period.

The null hypotheses to be tested are that the mean absolute change from study baseline in $ppFEV_1$ to the average of the Week 4 and Week 8 measurements is the same for (i) TEZ/IVA and placebo; and (ii) IVA monotherapy and placebo.

Assuming a standard deviation (SD) of 7 percentage points, 30 subjects per sequence are needed to have at least 90% power to detect a 3 percentage point treatment difference between TEZ/IVA and placebo when the mean values of the primary endpoint are being compared. A 2-sided significance level of 0.05 was used in the sample size calculations. Accounting for the testing strategy, the proposed sample size will yield approximately an 85% chance of observing a statistically significant difference between IVA monotherapy and placebo for the primary endpoint, under the assumption that IVA monotherapy is also 3 percentage points better than placebo (refer to Section 8.3.2.3 for a detailed description of the testing strategy). The sample size estimate was based on 10,000 simulation runs with an incomplete block design assuming no dropouts. In the simulation, the correlation between responses to the 2 treatments within a subject was assumed to be zero. After adjusting for an assumed dropout rate of 10%, the sample size was increased to 34 subjects per sequence (204 total subjects).

6.3 Randomization

Approximately 204 subjects (34 per sequence) who meet eligibility criteria will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), $ppFEV_1$ severity determined during the Screening Period (<70 versus ≥70), and type of residual function mutation on the second CFTR allele (Class V non-canonical splice mutation versus Classes II to IV residual function mutation; see section 16 of the clinical study protocol), and then randomized (1:1:1:1:1:1) to 1 of the 6 treatment sequences, as shown in Section 6.1. A minimum of 25% of enrolled subjects will carry a Class II to IV mutation on the second CFTR allele (see Section 10.8). Enrollment into the non-canonical splice strata will be limited to no more than 75% of total enrollment.

An IWRS will be used to assign subjects to treatment sequence and to ensure enrollment of at least 25% of subject with Class II to IV residual function mutations. The IWRS will use 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
- Any site personnel for whom this information is important to ensure the safety of the subject and their fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy serious adverse event (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 unblindings 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 but 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 assessments 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 postdose 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 not 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.

[redacted]

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 without having successfully reached and discussed the situation with the medical monitor.

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 Global Patient Safety (GPS) or designee, per Section 13.1.2 of the clinical study protocol.

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 drug.

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 mutations (see Section 10.8) 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 for those randomized or exposed to study drug will be presented in data listings. The Schedule of Assessments is provided in Section 10.1. The precision standards are provided in Section 10.6.

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.

Treatment Emergent (TE) Period for Treatment Period 1 will correspond to data from the first dose of study drug in the first period to the safety evaluation visit (Safety Follow-up Visit, if subject discontinues treatment in Period 1) or 28 days after the last dose in the same period for subjects who do not have a safety evaluation visit. Similarly, the TE period for Treatment Period 2 will correspond to data from the first dose of study drug in the second period through the Safety Follow-up Visit (SFUV) or 28 days after the last dose in the same period for subjects who do not have an SFUV. The TE period for Treatment Period 1 and Treatment Period 2 will not exceed the day before the first dose of study drug in the extension study for subjects who enrolled into the extension study.

Baseline Value: For this crossover study, 2 types of baseline will be defined. The *study baseline* is defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in the study. The definition will be applied to all

demographics, background, and baseline characteristics and also to efficacy data analyses, including the primary endpoint analysis. In addition, *period baseline* is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in each Treatment Period. For Treatment Period 2, the baseline should be from an assessment measured after the TE period for Treatment Period 1. This definition will be applied to all safety data analysis. For ECG, baseline for Period 1 will be defined as the average of the 3 pretreatment measurements on Day 1. For sweat chloride, the study baseline value will be the mean of assessment values on the left and the right arm at the most recent time point prior to the first dose of study drug in the study. If the result from only one of the arms is available then the result from that arm will be considered as baseline.

Change (Absolute change) from study baseline will be calculated as post-baseline value – study baseline value.

Relative change from study baseline will be calculated as 100x (post-baseline value – study baseline value)/study baseline value.

Change (Absolute change) from period baseline will be calculated as post-baseline value – period baseline value.

Relative change from period baseline will be calculated as 100x (post-baseline value – period baseline value)/period baseline value.

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 10.2 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. If there are no measurements at the scheduled visit:
     - 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.

- A safety follow-up visit (SFUV) assessment will follow the windowing rules for regular visits if it falls within the upper boundary of the visit window for Week 8 (period 1) or Week 24 (period 2), or remain as SFUV otherwise.

– 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; 3) SFUV will not be windowed, instead, used per nominal visit in relevant analyses.

Note: spirometry assessments, BMI, weight, and height will be used for both efficacy and safety purposes. The corresponding measurements will follow visit windowing rules for efficacy.

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

Unless otherwise defined, the FAS will be used for all analyses of background data. The background analyses will be performed according to the treatment to which the subject was assigned in each period.

8.2.1 Subject Disposition

The number of subjects in the following categories will be presented by treatment group:

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

The number of subjects in the following categories will be presented by treatment group for each period (Period 1 and Period 2):

- Full Analysis Set (FAS)
- Safety Set

The number and percentage (based on Safety Set) of subjects in each of the following disposition categories will be presented by treatment group for each period (Period 1 and Period 2):

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

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

- Completed treatment regimen in both periods
- Completed study
- Rollover to extension

A listing will be provided for subjects who discontinued treatment or who discontinued 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 in each treatment sequence as the denominator. A randomization listing also will be provided.

8.2.2 Demographics and Baseline Characteristics

Demographic and study baseline characteristics data will be summarized by treatment group based on the FAS for each period (Period 1 and Period 2).

Demographic data will include the following:

- Age at screening
- Age group at screening (< 18, and ≥18 years)
- Sex
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other)
- Geographic region (North America and Europe)

Note: Australia and Israel will be presented under Europe.

Baseline characteristics will include the following:

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

Stratification categories will include the following:

- $ppFEV_1$ at screening (<70, and ≥70)
- Residual function mutation (Class V non-canonical splice, and Classes II to IV residual function)

Disease characteristics will include the following:

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

- ppFEV$_1$ at study baseline
- Sweat chloride at study baseline
- CFQ-R at study baseline
- FEV$_1$ (L) at study baseline
- FVC (L) at study baseline
- Percent predicted FVC at study baseline
- FEF$_{25-75\%}$ (L/sec) at study baseline
- Percent predicted FEF$_{25-75\%}$ at study baseline
- FEV$_1$/FVC at study baseline
- 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)
- Pancreatic Insufficient (defined as fecal elastase-1 value of <200 µg/g)

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 treatment group, system organ class (SOC) and preferred term (PT) for each period (Period 1 and Period 2). The corresponding data listing also will be provided.

In addition, the number of subjects reported to have had positive cultures for respiratory pathogens in 2 years prior to screening (i.e., answered yes on the respiratory microbiology form) will be summarized by test and subcategories within the test for each period. 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 follows:

- **Prior medication:** any medication that started before the first dose of study drug in the study, regardless of when it ended.
- **Concomitant medication:** medication continued or newly received during the TE period for Treatment Period 1 or Treatment Period 2. If a subject took a medication during a specific Treatment Period, this medication will be attributed to the treatment the subject received during this Treatment Period. As a result, 1 medication could be attributed to more than 1 study drug for an individual subject.
- **Post-treatment medication:** medication continued or newly received after the TE period for Treatment Period 2, or between the TE periods for Treatment Period 1 and Treatment Period 2, or after the TE period for Treatment Period 1 for subjects who do not have Treatment Period 2.

A given medication can be classified as a prior medication, a concomitant medication, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether the medication was taken before initial dosing, concomitantly, or post-treatment, it will be considered as prior, concomitant, and post-treatment.

For the FAS, prior medications and concomitant medications will be summarized descriptively by: 1) treatment group, preferred name (PN); and 2) treatment group, anatomic class (ATC) level 1, ATC level 2, and PN. Prior medication summaries will be by period (Period 1 and Period 2). Post-treatment medications will be listed for each subject.

As an intermediate step for programming purposes, medications with missing or partially missing start dates will use 2000 to impute for the missing year, January for the missing month, and 1 for the missing day. Medications with missing or partially missing stop dates will use 2050 to impute for the missing year, December for the missing month, and the last day of the month for the 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 start date	Medication end date				
	< Start date of TE Period 1	≥ Start date of TE Period 1 and ≤ End date of TE Period 1	> End date of TE Period 1 and < Start date of TE Period 2	≥ Start date of TE Period 2 and ≤ End date of TE Period 2	> End date of TE Period 2
< Start date of TE Period 1	P	PC1	PC1A	PC1C2A	PC1C2A
≥ Start date of TE Period 1 and ≤ End date of TE Period 1	-	C1	C1A	C1C2A	C1C2A
> End date of TE Period 1 and < Start date of TE Period 2	-	-	A	C2A	C2A
≥ Start date of TE Period 2 and ≤ End date of TE Period 2	-	-	-	C2	C2A
> End date of TE Period 2	-	-	-	-	A

P – Prior; C1 – Concomitant for the Treatment in Period1; C2 – Concomitant for the Treatment in Period 2; A – Post-Treatment.

8.2.5 Study Drug Exposure

Exposure summaries will be based on the FAS and presented by treatment group.

Duration of study drug exposure is defined as follows: last dose date – first dose date + 1 day within the treatment period, 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 weeks. Additionally, the total duration of study drug exposure, defined as the total of duration of study drug exposure of all subjects and expressed in patient years, will be provided.

8.2.6 Study Drug Compliance

Study drug compliance will be measured by the compliance rate; summarized based on the FAS and presented by treatment group.

Compliance rate will be calculated as follows:

$$100 \times [1 - (\text{Total number of days study drug interrupted}) / (\text{Duration of study drug exposure})].$$

The total number of days study drug interrupted is defined as the total of number of days the study drug was interrupted in each interruption interval; where number of days 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% 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. IPD rules will be developed and finalized before database lock.

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

- Violation of subjects rights, safety or well-being
- 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 sequence. Additionally, IPDs will be provided as a subject data listing.

8.3 Efficacy Analysis

The primary objective of this study is to evaluate the efficacy of TEZ/IVA and IVA monotherapy. For efficacy analysis, the statistical inference will be based on change from study baseline. Unless otherwise defined, all efficacy analyses described in this section will use the FAS. The efficacy analyses will be performed according to the treatment to which the subject was assigned in each period. Data for a period will be used provided that the subject received at least one dose of study drug in that treatment period.

8.3.1 Analysis of Primary Efficacy Endpoint

The analysis will include all available measurements up to Week 8 [inclusive] during each treatment period, both on-treatment measurements and measurements after treatment discontinuation, per the visit windowing rules (Section 8.1).

8.3.1.1 Definition of Primary Efficacy Endpoint

The primary efficacy endpoint is the absolute change in $ppFEV_1$ from study baseline to the average of the Week 4 and Week 8 measurements in each of the two Treatment Periods.

$ppFEV_1$ 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 10.3.

8.3.1.2 Primary Analysis of Primary Efficacy Endpoint

The primary efficacy analysis will be based on a mixed effects model using SAS procedure MIXED. The null hypotheses to be tested are that the mean absolute change from study baseline in $ppFEV_1$ to the average of the Week 4 and Week 8 measurements is the same for (i) TEZ/IVA and placebo and (ii) IVA monotherapy and placebo.

The primary analysis model will include the absolute change from study baseline in $ppFEV_1$ to the average of the Week 4 and Week 8 measurements as the dependent variable and the following fixed effects: treatment, period, $ppFEV_1$ at study baseline, and subject as a random effect. The within-subject covariance will be assumed to have the same compound symmetry (CS) structure for sequences containing placebo treatment but will be different from the CS structure for sequences containing active treatment in both periods. Denominator degrees of

freedom for the F-test for fixed effects will be estimated using the Kenward-Roger approximation[3]. The estimated mean of the dependent variable, a 95% confidence interval, and a 2-sided *P* value will be provided for each treatment. Similarly, the estimated between group treatment differences along with the corresponding 95% CI and 2-sided *P* values will be presented.

No imputation of missing data will be performed. Subjects who have data only for one of the periods will have a data structure similar to a parallel-group trial. Assuming that these subjects have dropped out at random, an estimate of treatment effect based on such subjects will be combined with the estimate from subjects who have data in both treatment periods with weights based on the precision of these estimates[4].

The drop-out rate is expected to be low based on the experience with other CF studies (for example, drop-out rate in Study VX12-809-103 was 4.6%, Study VX12-809-104 was 5.2% and Study VX12-770-111, a crossover study, was 7.7%). Note that carryover effects are not included in the model; such effects are not expected because of the long washout period.

The SAS code to implement the primary analysis will be similar to the code presented below:

```
proc mixed data=xxx;
    class subject period treatment group;
    model primary efficacy endpoint = period treatment
              ppFEV1 at study baseline/ddfm=KR;
    repeated period/sub=subject type=cs group=group;
    lsmeans treatment / pdiff cl;
run;
```

where "primary efficacy endpoint" is the average absolute change from study baseline in $ppFEV_1$ at weeks 4 and 8 in each treatment period. The Group= statement will specify the variable so that the covariance structure will be different for each value of the variable.

Descriptive statistics associated with the raw value and the absolute change from study baseline in $ppFEV_1$ at post-baseline visits (Day 15, Weeks 4, and 8) along with the average $ppFEV_1$ at Weeks 4 and 8 and the average absolute change from study baseline in $ppFEV_1$ at Weeks 4 and 8 will be summarized by treatment group. Subjects with missing $ppFEV_1$ at both Week 4 and Week 8 visits will have missing average $ppFEV_1$ at Weeks 4 and 8. Therefore, they will not be included in the related summaries. The cumulative distribution of the average absolute change from study baseline in $ppFEV_1$ at Weeks 4 and 8 in each treatment period will be plotted by treatment group.

In addition, analysis based on an ANCOVA model using absolute change from study baseline in $ppFEV_1$ to the average of the Week 4 and Week 8 measurements from Treatment Period 1 will be performed to assess the treatment effect difference in case there is a carryover effect. The resulting model will include treatment, age group at screening (<18 vs. ≥18 years old), $ppFEV_1$ at study baseline and category of residual function mutation (Class V non-canonical splice mutation versus Classes II to IV residual function mutation). The estimated mean of the dependent variable for each treatment and between treatment differences will be presented along with the 95% CI.

[redacted]

8.3.2 Analysis of Secondary Efficacy Endpoints

The following is a key secondary efficacy endpoint:

1. Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period

The study also has the following other secondary efficacy endpoints:

2. Relative change in ppFEV$_1$ from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period
3. Absolute change in sweat chloride from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period

8.3.2.1 Definition of Secondary Efficacy Endpoints

8.3.2.1.1 Key Secondary Efficacy Endpoint

Absolute Change in CFQ-R respiratory domain score from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period

The absolute change from study baseline in the respiratory domain of the CFQ-R (Pooled 'Children Ages 12 and 13' Version and 'Adolescents and Adults' Version) to the average of Week 4 and Week 8 measurements in each treatment period will be analyzed based on the *CFQ-R scaled scores* described below.

The CFQ-R[6,7,8] is a validated CF-specific instrument that measures quality-of-life domains. This study uses three different versions of CFQ-R forms:

- 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 10.4.

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
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

Relative change in ppFEV$_1$ from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period

The calculations of ppFEV$_1$ and the relative change from study baseline will follow the definitions in Section 8.3.1.1 and Section 8.1.

Absolute change in sweat chloride from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period

Sweat chloride will be collected at baseline and 2 post-baseline time points (Weeks 4 and 8) in each treatment period. Values > 160 mmol/L or < 10 mmol/L will be set to missing and excluded from the analysis.

Absolute change from study 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.

8.3.2.2 Analysis of Key Secondary Efficacy Endpoint

Absolute change in CFQ-R respiratory domain score from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period

Analysis for the absolute change from study baseline in CFQ-R respiratory domain (Pooled 'Children Ages 12 and 13' Version and 'Adolescents and Adults' Version) score to the average of Week 4 and Week 8 scores in each treatment period will be similar to the primary analysis of the primary efficacy endpoint. However, ppFEV$_1$ at study baseline will be replaced by CFQ-R respiratory domain score at study baseline in the model.

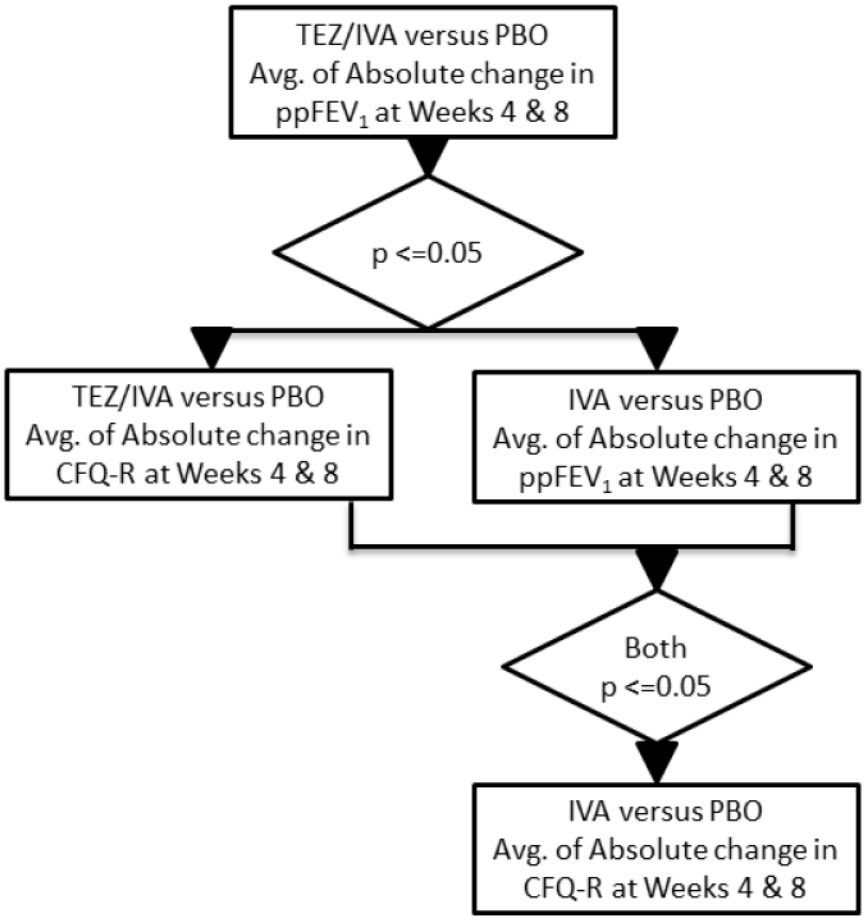
The estimated mean of absolute change from study baseline in CFQ-R respiratory domain score to the average of Week 4 and Week 8 scores will be presented along with the 95% CI and the 2-sided *P* value. Similarly, the estimated differences between treatment groups and the associated 95% CI and *P* value will be presented.

The raw value and absolute change from study baseline in CFQ-R respiratory domain score at post-baseline visits (Weeks 4 and 8) will be summarized by treatment group using descriptive statistics. Similar descriptive statistics will also be presented for average CFQ-R respiratory domain score at Weeks 4 and 8 and the average absolute change from study baseline in CFQ-R respiratory domain score at Weeks 4 and 8. The cumulative distribution plot will be created for this endpoint.

8.3.2.3 Multiplicity Adjustment

There are 3 potential treatment comparisons for the primary and key secondary endpoint: TEZ/IVA versus placebo, IVA monotherapy versus placebo, and TEZ/IVA versus IVA monotherapy. The testing strategy will be limited to the comparison of TEZ/IVA versus placebo and IVA monotherapy versus placebo. To control for multiplicity of endpoints and treatments (the probability of Type 1 error), each endpoint will be assessed sequentially using a gatekeeping approach where statistical significance can be claimed for the key secondary endpoint only if the primary endpoint meets the requirements for significance. Additionally, as there are two treatments for each endpoint, the gatekeeping approach will also be applied, i.e., IVA monotherapy for a given endpoint can achieve significance only if the comparison for TEZ/IVA for the same endpoint is significant (Figure 8-1). For each endpoint, and for each treatment group, the comparison with placebo will be conducted using a significance level (alpha) set at 0.05 (2-sided).

Figure 8-1 Testing Strategy for the Primary and Key Secondary Endpoint



IVA: ivacaftor; TEZ: VX-661; PBO: placebo; ppFEV1: percent predicted forced expiratory volume in 1 second; CFQ-R: Cystic Fibrosis Questionnaire–Revised (respiratory domain); Avg: Average

8.3.2.4 Analysis of Other Secondary Efficacy Endpoints

Relative change in ppFEV$_1$ from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period

Analysis of this variable will be similar to the primary analysis of the primary efficacy endpoint.

The estimated mean of relative change from study baseline in ppFEV$_1$ to the average of Week 4 and Week 8 measurements will be presented along with the 95% CI and the 2-sided *P* value. Similarly, the estimated differences between treatment groups and the associated 95% CI and *P* value will be presented.

In addition, summary statistics of the relative change from study baseline in ppFEV$_1$ at post baseline visits (Day 15, Week 4 and 8) as well as the average relative change from study baseline in ppFEV$_1$ at Weeks 4 and 8 will be presented by treatment group. The cumulative distribution plot will not be created for this endpoint.

Absolute change in sweat chloride from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period

Analysis of this variable will be similar to the primary analysis of the primary efficacy endpoint. However, ppFEV$_1$ at study baseline will be replaced by sweat chloride at study baseline in the model.

The estimated mean of absolute change from study baseline in sweat chloride to the average of Week 4 and Week 8 measurements will be presented along with the 95% CI and the 2-sided *P* value. Similarly, the estimated differences between treatment groups and the associated 95% CI and *P* value will be presented.

In addition, raw value and absolute change from study baseline in sweat chloride at post-baseline visits (Weeks 4 and 8) along with the average sweat chloride at Weeks 4 and 8 and the average absolute change from study baseline in sweat chloride at Weeks 4 and 8 will be summarized by treatment group using descriptive statistics. The cumulative distribution plot will not be created for this endpoint.

8.3.2.5 Sensitivity, Supportive, and Subgroup Analysis of Secondary Endpoints

No sensitivity, supportive, or subgroup analysis are planned for the secondary endpoints.

[redacted]

[redacted]

8.4 Safety Analysis

All safety analyses will be based on the set of data associated with the TE period for Treatment Period 1 and the TE period for Treatment Period 2. Safety analyses will use the Safety Set. Subjects will be analyzed according to the treatment they actually received in a given treatment period. For subjects receiving study drug from more than one treatment group in the same treatment period, the treatment group allocation will be the higher treatment group (TEZ/IVA > IVA monotherapy > Placebo). For safety analysis, the period baseline will be used.

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 (in subjects <18 years at screening).

The safety profile will also include the following safety-supporting data

- predose ppFEV$_1$ and FEV$_1$ (L) across visits
- Weight
- BMI.

Only descriptive analysis of safety will be performed; no statistical testing is planned.

For the purpose of safety analysis, the study period will be further divided into 3 segments per the definition of the treatment emergent (TE) period (Section 8.1):

- The **pre-treatment period** is the period after the informed consent/assent date and before the initial dosing of study drug in the study.
- The **treatment-emergent period** (TE period) is defined in Section 8.1.
- The **post-treatment period** is the period after the last date of TE period for Treatment Period 2 to the date of the last study record in the clinical database or the period between the end of TE period for Treatment Period 1 and the start of TE period for Treatment Period 2. For subjects who do not have Treatment Period 2, the period after the last date

of TE period for Treatment Period 1 to the date of the last study record in the clinical database will be considered as post-treatment period.

8.4.1 Adverse Events

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

- **Pretreatment AE:** any AE that started before initial dosing of study drug in the study.
- **TEAE:** any AE that increased in severity or that was newly developed during the TE period for Treatment Period 1 or Treatment Period 2. If an AE started (or increased in severity) during a specific Treatment Period, this AE will be attributed to the treatment the subject was receiving during the Treatment Period.
- **Post-treatment AE:** any AE that increased in severity or that was newly developed beyond the TE period for Treatment Period 2, or between the TE periods for Treatment Period 1 and Treatment Period 2, or beyond the TE period for Treatment Period 1 for subjects who do not have Treatment Period 2.

For AEs with missing or partial start date, if there is no clear evidence that the AEs started (or increased in severity) before the first dose, the start date will be imputed to the first dosing date and the AE assigned to the treatment in Treatment Period 1. As an intermediate step for programming purposes, imputation rules for missing or partially missing AE start/end dates are defined in Section 10.7.

By relationship to the study drug regimen, 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):** 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 Treatment Emergent AEs

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

- Any TEAEs
- TEAEs by relationship
- Related TEAEs
- TEAEs by severity
- Grade 3/4 TEAEs
- Serious TEAEs
- Related Serious TEAEs
- TEAEs leading to treatment discontinuation (this will include TEAEs leading to discontinuation of either TEZ/IVA tablet or the IVA tablet)
- TEAEs leading to treatment interruption (this will include TEAEs leading to interruption of either TEZ/IVA tablet or the IVA tablet)
- TEAEs leading to death

8.4.1.2 TEAEs and TE SAEs by System Organ Class and Preferred Term

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 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. TE SAEs will be summarized similarly.

8.4.1.4 Related TEAEs and TE SAEs by SOC, PT

The number and percentage of subjects with related TEAEs will be summarized by treatment group, SOC, 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. TEAEs in the following relationship to study drug regimen categories will be considered as related: Related, Possibly Related and Missing. TE SAEs will be summarized similarly.

8.4.1.5 Grade 3/4 TEAEs by SOC, PT

The number and percentage of subjects with Grade 3/4 TEAEs will be summarized by treatment group, SOC, 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. Grade 3/4 TEAEs include severe and life-threatening adverse events.

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 PT.

8.4.1.7 Elevated Transaminase

The following AE PTs 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 PT.

8.4.1.8 Summaries of Respiratory Events, Respiratory Symptoms and Elevated Transaminase by Treatment Interval

Respiratory events, Respiratory symptoms and elevated transaminase will also be summarized by the following treatment interval:

0-1 Weeks: [Day1, Day7]

>1 -2 Weeks: [Day8, Day14]

>0 -8 Weeks: [Day1, Day56]

>8 Weeks: [Day57, end of TE period])

8.4.1.9 Subgroup Analysis

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

- Age at screening (<18, ≥18 years)
- $ppFEV_1$ at study baseline (<40, ≥40 to <70, ≥70)
- Sex
- Residual function mutation (Class V non-canonical splice, Classes II to IV residual function)
- Region (North America, Europe)

Furthermore, TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, and TEAEs leading to death will be summarized by SOC and PT. In addition, a listing containing individual subject adverse event data for TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, SAEs and all deaths will be provided separately, with a flag indicating the TE status for SAEs and deaths.

For all AEs, the CRF captures the action taken for TEZ/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 IVA monotherapy) are different. The summaries and listings of "TEAEs Leading to Treatment Discontinuation" and "TEAEs 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 period 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, coagulation and chemistry measurements, the number and percentage of subjects with an abnormal low (<LLN) value and an abnormal high (>ULN) value at each analysis visit will be summarized.

The number and percentage of subjects with hematology, chemistry and coagulation values meeting the defined threshold criteria during the visit window for analysis visits will be summarized by analysis visit. Similarly, the hematology, chemistry and coagulation values meeting the defined threshold criteria during the overall TE period will be presented. The threshold analysis criteria are provided in Section 10.5 (Table 10-7 and Table 10-8).

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 during the TE period with elevated LFT will be included.
- For each of the LFTs, mean values (±SD) will be plotted by visit.
- The incidence of LFTs meeting threshold analysis criteria during the TE period against the period baseline threshold criteria will be summarized by treatment group (only worsening of the shift from period 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 period baseline to the value at Week 8 will be presented by treatment group for vitamin levels and lipid panel. A box plot of vitamin levels and lipid panel will also be plotted against visit.

For amylase and lipase, mean values (±SD) will be plotted by visit.

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

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 measurements meeting the threshold analysis criteria during the visit window for analysis visits will be summarized by analysis visit. Similarly, the ECG measurements meeting the threshold analysis criteria during the

overall TE period will be presented. The threshold analysis criteria are provided in Section 10.5 (Table 10-9).

8.4.4 Vital Signs

The raw values and change from period baseline values will be summarized by treatment group at each scheduled time point for the following treatment-emergent vital signs measurements: systolic and diastolic blood pressure (mm Hg), body temperature (°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 the threshold analysis criteria during the visit window for analysis visits will be summarized by analysis visit. Similarly, the vital signs meeting the threshold analysis criteria during the overall TE period will be presented. The threshold analysis criteria are provided in Section 10.5 (Table 10-10).

8.4.5 Pulse Oximetry

For treatment-emergent pulse oximetry measurements, a summary of raw values and change from period baseline values will be provided by treatment groups 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 period baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the TE period will be tabulated by treatment groups. Note: Normal oxygen saturation is defined as >95% and low oxygen saturation is defined as <=95%.

8.4.6 Postdose Spirometry

For the 2-hour and 4-hour postdose measurements on Day 1 and Day 15 of each treatment period, a summary of raw values for $ppFEV_1$ will be provided by treatment group at each time point. The absolute change from the predose value of $ppFEV_1$ on the same day will be provided by treatment at each time point. 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 addition, the number and percentage of subjects with (i)$ppFEV_1$ decline $\geq$10, $\geq$15, and $\geq$20 percentage points in the absolute change from the predose value (ii) FEV_1 decline of $\geq$0.2 L will be summarized by treatment group and by assessment day and time.

8.4.7 Physical Examination

Abnormal physical examination findings will be presented in a data listing.

8.4.8 Ophthalmologic Examination

Ophthalmologic examination findings will be presented in a data listing.

8.5 Safety Supportive Endpoints

8.5.1 Predose Spirometry

As supportive safety data, the following summaries regarding the decline in predose spirometry will be provided:

- Number and percentage of subjects with ≥10, ≥15 or ≥20 percentage points decrease in absolute change from period baseline in $ppFEV_1$ at each post-baseline visit.
- Number and percentage of subjects with ≥0.2 L decrease in absolute change from period baseline in FEV_1 at each post-baseline visit.

Subjects with ≥10 percentage points decrease in absolute change from period baseline in $ppFEV_1$ or ≥0.2 L decrease in the absolute change from period 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 visit from the period in which the decline criteria was met.

8.5.2 Weight and BMI

As supportive safety data, the following summaries will be provided:

- Number and percentage of subjects with a ≥3.0 kg or ≥6.0 kg decrease in absolute change from period baseline in weight at each post-baseline visit.
- Number and percentage of subjects with a ≥1.5 kg/m^2 or ≥3.0 kg/m^2 decrease in absolute change from period baseline in BMI at each post-baseline visit.

Subjects with ≥3.0 kg decrease in absolute change from period baseline in weight or ≥1.5 kg/m^2 decrease in the absolute change from period baseline in BMI will be listed. The listing will include raw values and absolute changes from period baseline in weight and BMI at each visit from the period in which the decline criteria was met.

8.6 [redacted]

[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) will be formed before study initiation. The IDMC's objectives and operational details will be defined in a separate document (IDMC Charter) which will be finalized before the first subject is screened in the study. The IDMC will conduct regular planned safety reviews of study data as outlined in the IDMC Charter and IDMC Analysis Plan.

10 APPENDICES

10.1 Schedule of Assessments

Table 10-1 Screening Period Assessments

Event/Assessment	Screening Period (Day -28 Through Day -1)
ICF and assent (when applicable)	X
Demographics	X
Medical history	X
Ophthalmological history	X
CFTR genotype[a]	X
CFQ-R[b]	X
[redacted]	[redacted]
Height and weight[c]	X
Ophthalmologic examination[d]	X
Complete PE	X
FSH[e]	X
Serum pregnancy test (all females of childbearing potential)[f]	X
Standard digital ECG[g]	X
Vital signs[h]	X
Pulse oximetry[h]	X
Spirometry[i]	X
Sweat chloride[j]	X
Urinalysis	X
Hematology	X
Coagulation	X
Serum chemistry	X

[a] All subjects will be tested for CFTR genotype and results must be confirmed before randomization. Specific instructions will be provided in the Laboratory Manual.

[b] CFQ-R and [redacted] must be completed prior to the start of any other assessments scheduled at that visit.

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

[d] 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 or if there is a documentation of bilateral lens removal (Section 11.7.8 of the CSP). Subjects with clinically significant cataracts, lens opacity, Y-suture, or lamellar rings will be excluded.

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

[f] 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.

[g] A standard digital ECG will be performed after the subject has been supine for at least 5 minutes.

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

[i] Spirometry may be performed pre- or post-bronchodilator (Section 11.6.1 of the CSP). Screening spirometry evaluation may be repeated, as specified in Section 8.1.1.1 of the CSP.

j A sweat chloride test must be performed if an eligible sweat chloride value is not available in the subject's medical records. For subjects using a sweat chloride value documented in their medical record to establish eligibility, the sweat chloride test at the Screening Visit is optional.

Table 10-1 Screening Period Assessments

Event/Assessment	Screening Period (Day -28 Through Day -1)
[redacted]	[redacted]
[redacted]	[redacted]
Inclusion/exclusion criteria review	X
Prior and concomitant medications	X
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: Cystic Fibrosis Questionnaire-Revised; CFTR: CF transmembrane conductance regulator; ECG: electrocardiogram; FSH: follicle-stimulating hormone; ICF: informed consent form; [redacted] PE: physical examination; SAE: serious adverse event; [redacted]

[k] One stool sample will be collected at the clinic or by the subject at home and provided before randomization

Table 10-2 Treatment Periods, Washout Period, ETT, and Safety Follow-up Visit Assessments

Event/Assessment[b]	Treatment Period 1				Washout[a]	Treatment Period 2				ETT Visit[c]	Safety Follow-up Visit 28 days (± 7 days) After Last Dose[d]
	Week 1 (Day 1)	Week 2 (Day 15) (± 3 Days)	Week 4 (Day 29) (± 5 Days)	Week 8 (Day 57) (± 5 Days)	Safety Evaluation Visit Week 12 (Day 85) (± 5 Days)	Week 17[a] (Day 113)	Week 18 (Day 127) (± 3 Days)	Week 20 (Day 141) (± 5 Days)	Week 24 (Day 169) (± 5 Days)		
Clinic visit	X	X	X	X	X	X	X	X	X	X	X
Inclusion and exclusion criteria review	X					X[e]					
CFQ-R[f]	X		X	X	X	X		X	X	X	X
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Height and weight[g]	X	X	X	X	X	X	X	X	X	X	X

[a] The Washout Period starts the day after completion of the Week 8 Visit and continues for 8 weeks (+7 days). The Washout Period is considered to be complete when dosing has occurred at the Week 17 Visit.

[b] 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 prematurely discontinue study drug treatment will continue to complete all other scheduled study visits for assessments of efficacy (spirometry, sweat chloride, and CFQ-R) and [redacted] through the end of the Treatment Period in which discontinuation occurred, as described in Section 8.1.6 of Clinical Study Protocol.

[c] If the subject prematurely discontinues study drug treatment, an ETT Visit should be scheduled as soon as possible after the decision to terminate study treatment. Subjects who prematurely discontinue study drug 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 Section 8.1.5 and 8.1.6 of Clinical Study Protocol.

[d] The Safety Follow-up Visit is not required for subjects who complete the Week 24 Visit and have enrolled in an extension study of TEZ in combination with IVA within 28 days after the last dose of study drug.

[e] In order to continue in Treatment Period 2, subjects must not have an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before the Week 17 Visit (first dose of study drug in Treatment Period 2) and must not have any "non-CF-related" illness within 2 weeks before the Week 17 Visit. "Illness" is defined as an acute (serious or nonserious) condition (e.g., gastroenteritis). If the subjects do not meet these criteria, then the continuation of the subjects into Treatment Period 2 must be discussed with the Medical Monitor.

[f] All questionnaires must be completed before the start of any other assessment scheduled for that visit. The CFQ-R must be completed first, followed by the [redacted] Subjects will need to complete a CFQ-R and [redacted] at the ETT Visit (Section 8.1.6 of Clinical Study Protocol).

[g] 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 10-2 Treatment Periods, Washout Period, ETT, and Safety Follow-up Visit Assessments

Event/Assessment[b]	Treatment Period 1				Washout[a]	Treatment Period 2				ETT Visit[c]	Safety Follow-up Visit 28 days (± 7 days) After Last Dose[d]
	Week 1 (Day 1)	Week 2 (Day 15) (± 3 Days)	Week 4 (Day 29) (± 5 Days)	Week 8 (Day 57) (± 5 Days)	Safety Evaluation Visit Week 12 (Day 85) (± 5 Days)	Week 17[a] (Day 113)	Week 18 (Day 127) (± 3 Days)	Week 20 (Day 141) (± 5 Days)	Week 24 (Day 169) (± 5 Days)		
Ophthalmologic examination[h]										X	X
Complete PE[i]	X					X					
Pregnancy test[j]	urine	urine	urine	serum	urine	urine	urine	urine	serum	serum	serum
Standard digital ECG[k]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[l]	X	X	X	X	X	X	X	X	X	X	X
Pulse oximetry[l]	X	X	X	X	X	X	X	X	X	X	X
Spirometry[m]	X	X	X	X	X	X	X	X	X	X	X
Sweat chloride[n]	X		X	X		X		X	X		
Urinalysis	X			X	X	X			X	X	X

[h] Subjects < 18 years of age at screening who discontinue study drug treatment after receiving at least 1 dose of study drug, and subjects < 18 years of age at screening who complete treatment but do not enroll in a separate extension study of TEZ/IVA within 28 days after the last dose of study drug will have an ophthalmologic exam conducted by a licensed ophthalmologist (see Section 11.7.8 of Clinical Study Protocol). 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 have documented bilateral lens removal do no need an ophthalmologic exam.

[i] In addition to the complete PEs indicated, symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

[j] Pregnancy tests will be performed for all female subjects of childbearing potential.

[k] All standard digital ECGs will be performed before dosing and after the subject has been supine for at least 5 minutes. At the Week 1, Week 2, Week 17, and Week 18 Visits, ECGs will be collected before dosing and at 1.5, 3, 4, and 6 hours after the morning dose. At the Week 1, Week 2, Week 17, and Week 18 visits the 4-hour postdose ECG will be collected before the 4-hour postdose spirometry assessment. The predose ECGs collected at the Week 1 (Day 1) visit 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.

[l] 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.

[m] At all visits, spirometry must be performed for all subjects before dosing and should be performed prebronchodilator (Section 11.6.1 of Clinical Study Protocol). At Week 1, Week 2, Week 17, and Week 18, subjects < 18 years of age at the Screening Visit will have additional spirometry performed at 2 and 4 hours after the morning dose. If more than 1 spirometry assessment is required at a visit, bronchodilators will be withheld until completion of the last scheduled spirometry assessment is completed.

[n] The Sweat collection on dosing visits should occur approximately 1 hour before the PK sample collection and before the morning dose of the study drugs. Sweat collection will not overlap with any other study assessments (Section 11.6.2 of Clinical Study Protocol).

Table 10-2 Treatment Periods, Washout Period, ETT, and Safety Follow-up Visit Assessments

Event/Assessment[b]	Treatment Period 1				Washout[a]	Treatment Period 2					
	Week 1 (Day 1)	Week 2 (Day 15) (± 3 Days)	Week 4 (Day 29) (± 5 Days)	Week 8 (Day 57) (± 5 Days)	Safety Evaluation Visit Week 12 (Day 85) (± 5 Days)	Week 17[a] (Day 113)	Week 18 (Day 127) (± 3 Days)	Week 20 (Day 141) (± 5 Days)	Week 24 (Day 169) (± 5 Days)	ETT Visit[c]	Safety Follow-up Visit 28 days (± 7 days) After Last Dose[d]
Hematology[o]	X	X	X	X	X	X	X	X	X	X	X
Coagulation[o]	X			X	X	X			X	X	X
Serum chemistry[o]	X	X	X	X	X	X	X	X	X	X	X
Lipid panel[p]	X			X		X			X	X	
Vitamin levels (A, D, E, K, B12)	X			X		X			X	X	
[redacted]											
[redacted]											
[redacted]											
PK sampling[u]			X	X				X	X	X	X
[redacted]											
[redacted]											
[redacted]											
[redacted]											

[o] Blood samples will be collected before the first dose of study drug.

[p] Subjects will require 4 hours of fasting before the blood sample for the lipid panel is obtained.

[q] [redacted]

[t] The samples may be collected at the study center during the study visit or may be collected by the subject at home and brought to the study visit.

[u] PK blood samples will be collected pre-morning-dose at Week 4, Week 8, Week 20, and Week 24. If study drug is not administered at the visit (i.e., study drug interruption or permanent discontinuation of study drug), a PK blood sample will still be collected. At the ETT and the Safety Follow-up Visit (as applicable), a PK blood sample will also be collected.

Table 10-2 Treatment Periods, Washout Period, ETT, and Safety Follow-up Visit Assessments

Event/Assessment[b]	Treatment Period 1				Washout[a]	Treatment Period 2				ETT Visit[c]	Safety Follow-up Visit 28 days (± 7 days) After Last Dose[d]
	Week 1 (Day 1)	Week 2 (Day 15) (± 3 Days)	Week 4 (Day 29) (± 5 Days)	Week 8 (Day 57) (± 5 Days)	Safety Evaluation Visit Week 12 (Day 85) (± 5 Days)	Week 17[a] (Day 113)	Week 18 (Day 127) (± 3 Days)	Week 20 (Day 141) (± 5 Days)	Week 24 (Day 169) (± 5 Days)		
Randomization[w]	X										
Meal(s) or snack(s) at site[x]	X	X	X			X	X	X			
Study drug dosing[y]	X	X	X			X	X	X			
Study drug count		X	X	X			X	X	X	X	
Concomitant medications[z]	X	X	X	X	X	X	X	X	X	X	X
Concomitant treatments and procedures	X	X	X	X	X	X	X	X	X	X	X
AEs and SAEs	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: Cystic Fibrosis Questionnaire–Revised; DNA: deoxyribonucleic acid; ECG: electrocardiogram; ETT: Early Treatment Termination; Eval: evaluation; ICF: informed consent form; [redacted] IWRS: interactive web response system; [redacted]; PE: physical examination; PK: pharmacokinetic; SAE: serious adverse event; [redacted]

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v [redacted]

w 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.

x 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.

y The study drug should be administered every 12 hours (± 2 hours) within 30 minutes after 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 in Treatment Period 1 will be administered the evening before the Week 8 Visit. The final dose of study drug in Treatment Period 2 will be administered the evening before the Week 24 Visit.

z All concomitant medications are collected through the Safety Follow-up Visit for all subjects. For subjects who prematurely discontinue study drug treatment and are followed for certain efficacy assessments after the ETT Visit (see Section 8.1.6 of Clinical Study Protocol), concomitant antibiotic therapy for 'sinopulmonary signs/symptoms' are collected through the Week 24 Visit, as described in Section 11.6.4.5.1 of Clinical Study Protocol.

10.2 Analysis Visit Window Mapping Rules for Efficacy and Safety Measurements

Table 10-3 Visit Window Mapping Rules (within Period)

Assessments	Period – Visit	Analysis Visit	Target Study Day	Visit Window (in study days)
• Weight and height • Vital signs • Pulse oximetry • Labs ○ Chemistry ○ Hematology	1-Baseline	Baseline	1	[screening visit, pre-dose Day 1]
	1 – Day 15	Day 15	15	[1*, 22]
	1 – Week 4	Week 4	29	[23, 43]
	1 – Week 8	Week 8	57	[44, 71]
	1 - Week 12 (Safety Evaluation Visit)	Safety Follow-up Visit	NA	Use the nominal visit name†
	2 - Baseline	Baseline	1	[end of TE period for first period +1 , pre-dose Week 17]
	2 – Week 18	Day 15	15	[1*, 22]
	2 – Week 20	Week 4	29	[23, 43]
	2 – Week 24	Week 8	57	[44, 71]
	ETT		NA	Follow the individual visit window to be mapped to individual visits
	2 – Safety Follow-up Visit	Safety Follow-up Visit	NA	Use the nominal visit name†
CFQ-R	1-Baseline	Baseline	1	[screening visit, Day 1]
	1 - Week 4	Week 4	29	[1*, 43]
	1 - Week 8	Week 8	57	[44, 71]
	1 - Week 12 (Safety Evaluation Visit)	Safety Follow-up Visit	NA	Use the nominal visit name†
	2-Baseline	Baseline	1	[end of TE period for first period +1 , Week 17]
	2 - Week 20	Week 4	29	[1*, 43]
	2- Week 24	Week 8	57	[44, 71]
	ETT		NA	Follow the individual visit window to be mapped to individual visits
	2 - Safety Follow-up Visit	Safety Follow-up Visit	NA	Use the nominal visit name†
• Sweat Chloride [redacted]	1-Baseline	Baseline	1	[screening visit, pre-dose Day 1]
	1 - Week 4	Week 4	29	[1*, 43]
	1 - Week 8	Week 8	57	[44, 71]
	2-Baseline	Baseline	1	[end of TE period for first period +1 , pre-dose Week 17]
	2 - Week 20	Week 4	29	[1*, 43]
	2 - Week 24	Week 8	57	[44, 71]
	ETT		NA	Follow the individual visit window to be mapped to individual visits
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]	[redacted]	[redacted]	[redacted]
• Labs o Coagulation o Urinalysis	1-Baseline	Baseline	1	[screening visit, pre-dose Day 1]
	1 - Week 8	Week 8	57	[1*, 71]
	1 - Week 12 (Safety Evaluation Visit)	Safety Follow-up Visit	NA	Use the nominal visit name
	2-Baseline	Baseline	1	[end of TE period for first period +1 , pre-dose Week 17]
	2 - Week 24	Week 8	57	[1*, 71]
	ETT		NA	Follow the individual visit window to be mapped to individual visits
	2 - Safety Follow-up Visit	Safety Follow-up Visit	NA	Use the nominal visit name
• Labs o Vitamin levels o Lipid panel	1-Baseline	Baseline	1	[screening visit, pre-dose Day 1]
	1 - Week 8	Week 8	57	[1*, 71]
	2-Baseline	Baseline	1	[end of TE period for first period +1 , pre-dose Week 17]
	2 - Week 24	Week 8	57	[1*, 71]
	ETT		NA	Follow the individual visit window to be mapped to individual visits
• Spirometry • Standard 12-lead ECG	1-Baseline	Baseline	1	[screening visit, pre-dose Day 1]
	1 – Day 1 Predose and Postdose	Day 1	1	Nominal
	1 – Day 15 Predose and Postdose	Day 15	15	Nominal
		Day 15	15	[1*, 15] if no nominal Day 15
	1 – Week 4	Week 4	29	[Nominal Day 15+1, 43] if there is nominal Day 15; [16, 43] otherwise.
	1 – Week 8	Week 8	57	[44, 71]
	1 - Week 12 (Safety Evaluation Visit)	Safety Follow-up Visit	NA	Use the nominal visit name†
	2 - Baseline	Baseline	1	[end of TE period for first period +1 , pre-dose Week 17]
	2 – Week 17 Predose and Postdose	Day 1	1	Nominal
	2 – Week 18 Predose and Postdose	Day 15	15	Nominal
		Day 15	15	[1*, 15] if no nominal Week 18
	2 – Week 20	Week 4	29	[Nominal Week 18+1, 43] if there is nominal Week 18; [16, 43] otherwise.
	2 – Week 24	Week 8	57	[44, 71]
	ETT		NA	Follow the individual visit window to be mapped to individual visits
	2 - Safety Follow-up Visit	Safety Follow-up Visit	NA	Use the nominal visit name†

* only include day 1 post-dose measurements in each period
† for safety assessments use nominal visit and for efficacy assessments use nominal visit if visit day is greater than the upper boundary of the visit window for Week 8 (period 1) or Week 24 (period 2)

Note:

1. For spirometry and ECG data on Day 1 and Day 15 of each treatment period, no visit windowing rule shall be applied. Instead, nominal visit will be used.
2. On Day 1 of period 1, the pre-dose ECG measurements are collected as triplicates. The average of pre-dose triplicates will be used as baseline. Only the pre-dose assessments of the triplicate will be used for the baseline. If all the measurements for triplicates are missing or post-dose, the last non-missing pre-dose assessment will be used as the baseline.
3. 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.
    - Assessments at early treatment termination (ETT) visit will follow the windowing rules for regular visits up to Week 24.
    - A safety follow-up visit (SFUV) assessment will follow the windowing rules for regular visits if it falls within the upper boundary of the visit window for Week 8 (period 1) or Week 24 (period 2), or remain as SFUV otherwise.
4. For all safety parameters:
    - If there are multiple measurements within a visit window, 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. Spirometry, BMI, Weight and Height will follow the efficacy windowing rules.

10.3 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 10-4.

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 10-5 and Table 10-6.

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 10-4 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 10-5 WNVs Equation Coefficients by Sex and Age in White Boys and Girls

Sex	Age	FEV_1		FVC		$FEF_{25-75\%}$		FEV_1/FVC	
		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 10-6 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)

10.5 Threshold Analysis Criteria

Table 10-7 Threshold Criteria for Laboratory Tests

Parameter	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 >ULN - ≤ 2.9 mmol/L >2.9 – ≤ 3.1 mmol/L >3.1 – ≤ 3.4 mmol/L >3.4 mmol/L	CTCAE grade 1-4
	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 (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	FDA DILI Guidance
Alkaline Phosphatase	>ULN - ≤ 1.5xULN >1.5 – ≤ 2.5 xULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	FDA DILI Guidance 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	CTCAE grade 1-4

	<75.0 – ≥ 50.0 x 10e9 /L
	<50.0 – ≥ 25.0 x 10e9 /L
	<25.0 x 10e9 /L

Table 10-8 Threshold Criteria for Coagulation

Parameter	Criteria	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 10-9 Threshold Criteria for ECGs

Parameter	Criteria	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 10-10 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	809/770 analyses
	>90 mmHg	
	>100 mmHg	
	>5 mmHg increase from baseline	
	>10 mmHg increase from baseline	
	>90 mmHg and >5 mmHg increase from baseline	
	>90 mmHg and >10 mmHg increase from baseline	
	>100 mmHg and >5 mmHg increase from baseline	
	>100 mmHg and >10 mmHg increase from baseline	
	DBP decreased	
	<60 mmHg	
	<45 mmHg	
	>5 mmHg decrease from baseline	
	>10 mmHg decrease from baseline	
	<60 mmHg and >5 mmHg decrease from baseline	
	<60 mmHg and >10 mmHg decrease from baseline	
	<45 mmHg and >5 mmHg decrease from baseline	
	<45 mmHg and >10 mmHg decrease from baseline	
Weight	Weight gain	CTCAE grade 1-3
	≥5 % increase from baseline	
	≥10 % increase from baseline	
	≥ 20% increase from baseline	

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

10.6 Standards for Efficacy and Safety Variable Display in TFLs

Continuous Variables

The precision for continuous variables has been specified in the Vertex Standard Programming Rules document (Version 1.0, December 2015):

http://collab.vrtx.com/sites/biometrics/biostatistics/Documents/Standard%20Programming%20Rules_V1.0%20Final%20Dec%2017%202015.doc

The precision of the measurement in raw values for other continuous variables will be used to determine the number of decimal places to present in tables, figures, and derived listings. Minimum and maximum values will be reported with the same precision as the units of measure. The mean, median, and SD will be reported to 1 greater decimal place.

Categorical Variables: Percentages will be presented to 1 decimal place.

10.7 Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined 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 before 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 pretreatment 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 before 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 pretreatment AE, TEAE or post-treatment AE.

If Year of AE start date is missing:

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

The imputation rule will be applied with respect to treatment start date for both periods and preference will be given to treatment in period 1 in case the AE is assigned to treatments in both periods. Missing or partially missing AE end date will not be imputed.

10.8 Second CFTR Allele Mutations Included for Subjects who are Heterozygous for the F508del-CFTR Mutation

Per the study eligibility criteria, heterozygous *F508del-CFTR* subjects must have a second CFTR allele that encodes a mutation predicted to have residual function. Criteria for including a mutation are (1) having residual function based on population-level phenotypic data and (2) in vitro responsiveness to IVA. The criteria for clinical phenotype are average sweat chloride <86 mmol/L (1 standard deviation from the average sweat chloride for the most common processing and trafficking mutation, *F508del-CFTR*), and incidence of pancreatic insufficiency ≤50% based on subjects with at least 1 copy of the mutation from epidemiologic data or published literature. In vitro response to IVA was defined as an increase in percent normal chloride transport of ≥10 percentage points in transfected FRT cells expressing the CFTR form produced by the mutation. The list below represents eligible mutations.

***CFTR* Mutations Predicted to Have Residual Function and That May Be Responsive to IVA**

2789+5G→A	R74W	R352Q	R1070W
3849+10kbC→T	D110E	A455E	F1074L
3272-26A→G	D110H	D579G	D1152H
711+3A→G	R117C	S945L	D1270N
E56K	E193K	S977F	
P67L	L206W	F1052V	
E831X	R347H	K1060T	

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