VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX16-659-101 Version 3.0

A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-659 Combination Therapy in Subjects Aged 18 Years and Older With Cystic Fibrosis

Authors of SAP: [redacted]

Version: Version 1.0
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[redacted]

2 MODIFICATIONS

2.1 Modifications to the Approved Clinical Study Protocol

Key changes in the current version of the SAP are summarized below.

Change and Rationale	Affected Sections
Treatment-emergent (TE) period has been revised to be from first dose date of study drug in the Treatment Period until 28 days after the last dose date of study drug or end of study date (based on end of study visit in CRFs), whichever occurs first.	Section 8.1

2.2 Modifications to the Approved Statistical Analysis Plan

This is the 1st version of Statistical Analysis Plan for the final analysis.

2.3 Modifications to the Approved DMC Charter

Not Applicable.

3 INTRODUCTION

This statistical analysis plan (SAP) for the final analysis is based on the approved clinical study protocol (CSP), Version 3.0, dated 01 Sep 2017, approved electronic case report form (eCRF), Version 1.4, dated 10 Aug 2017, and approved eCRF completion guidelines, Version 1.0, dated 14 Jul 2017. This SAP will be used to perform interim analyses (IAs) for each part after 50% of subjects in the part have completed the Day 15 Visit. In addition, this SAP will be used to perform final analysis that will occur after all subjects in each part have completed the Safety Follow-Up Visit.

This is a Phase 2, randomized, double-blind, placebo- and TEZ/IVA-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of VX-659 combination therapy in subjects aged 18 years and older with cystic fibrosis.

This SAP (Methods) documents the planned statistical analyses of efficacy endpoints and safety endpoints.

Vertex Biometrics will perform the statistical analysis for each IA, and the final analysis. SAS® Version 9.4 or higher software [redacted] will be used to generate all statistical outputs (tables, figures, listings, and datasets).

The SAP (Methods) will be finalized and approved prior to the data cut for the first IA. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP prior to the clinical database lock for the final analysis. Any changes made to the SAP Methods after the clinical database lock has occurred will be documented in the clinical study report for this study.

4 STUDY OBJECTIVES

4.1 Primary Objective

Parts 1 and 2: To evaluate the safety and tolerability of VX-659 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA)

Part 3 (optional): To evaluate the safety and tolerability of VX-659 in TC with TEZ and VX-561 (also known as CTP-656, deuterated IVA)

All parts: To evaluate the efficacy of VX-659 in TC with TEZ and either IVA or VX-561

4.2 Secondary Objectives

Parts 1 and 2: To evaluate the pharmacodynamic (PD) effects of VX-659 in TC with TEZ and IVA on CFTR function

Part 3 (optional): To evaluate the PD effects of VX-659 in TC with TEZ and VX-561 on CFTR function

All parts:

- To evaluate the pharmacokinetics (PK) of VX-659 when administered in TC with TEZ and either IVA or VX-561
- To evaluate the PK of TEZ, IVA, VX-561 and their respective metabolites when administered with VX-659 (as applicable)

5 STUDY ENDPOINTS

5.1 Efficacy Endpoint

5.1.1 Primary Efficacy Endpoint

- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline through the Day 29 Visit

5.1.2 Secondary Efficacy Endpoints

- Absolute change in sweat chloride concentrations from baseline through the Day 29 Visit
- Relative change in $ppFEV_1$ from baseline through the Day 29 Visit
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline at the Day 29 Visit

5.2 Safety Endpoints

Safety and tolerability will be evaluated via the following endpoints:

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

6 STUDY DESIGN

6.1 Overall Design

This is a Phase 2, randomized, double-blind, placebo- and TEZ/IVA-controlled, parallel-group, 3-part, multicenter study. All parts will be conducted concurrently. Subjects may not participate in more than 1 part.

Key study elements of each part are summarized in Table 6-1, treatment arms and planned doses are shown in Table 6-2, and a schematic of the study design is shown in Figure 6-1. Study visits and assessments are shown in Table 11-1 (Part 1), Table 11-2 (Part 2), and Table 11-3 (Part 3).

Table 6-1 Key Study Elements by Part

Element	Part 1	Part 2	Part 3 (optional)
Study population			
Genotype(s)	F/MF	F/F	F/MF
Age	≥18 years	≥18 years	≥18 years
$ppFEV_1$ criteria	≥40 to ≤90	≥40 to ≤90	≥40 to ≤90
Number of subjects	Approximately 54	Approximately 27	Approximately 24
Randomization			
Ratio	1:1:2:2 (placebo:TC-low: TC-mid:TC-high)	1:2 (TEZ/IVA:TC-high)	1:3 (placebo:TC2-high)
Stratification	$ppFEV_1$ (<70, ≥70)	$ppFEV_1$ (<70, ≥70)	$ppFEV_1$ (<70, ≥70)

Table 6-1 Key Study Elements by Part

Element	Part 1	Part 2	Part 3 (optional)
Study design	Parallel group	Parallel group	Parallel group
Control	Placebo	TEZ/IVA	Placebo

F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a minimal *CFTR* function mutation that is not expected to respond to TEZ, IVA, or TEZ/IVA; IVA: ivacaftor; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TC: triple combination; TEZ: tezacaftor

Table 6-2 Treatment Arms and Planned Doses by Part

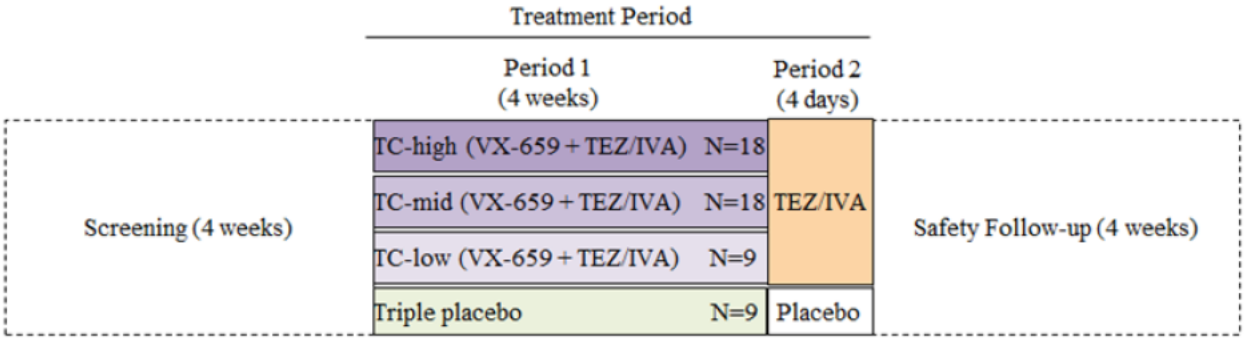
	Period 1			Period 2	
	VX-659 Dosage	TEZ Dosage	IVA Dosage	TEZ Dosage	IVA Dosage
Part 1					
TC-high	400 mg qd	100 mg qd	150 mg q12h	100 mg qd	150 mg q12h
TC-mid	240 mg qd	100 mg qd	150 mg q12h	100 mg qd	150 mg q12h
TC-low	80 mg qd	100 mg qd	150 mg q12h	100 mg qd	150 mg q12h
Triple placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Part 2[a]					
TEZ/IVA	Placebo	100 mg qd	150 mg q12h	100 mg qd	150 mg q12h
TC-high	400 mg qd	100 mg qd	150 mg q12h	100 mg qd	150 mg q12h
Part 3 (optional)					

	Period 1		
	VX-659 Dosage	TEZ Dosage	VX-561 Dosage
TC2-high	400 mg qd	100 mg qd	200 mg qd
Triple placebo	Placebo	Placebo	Placebo

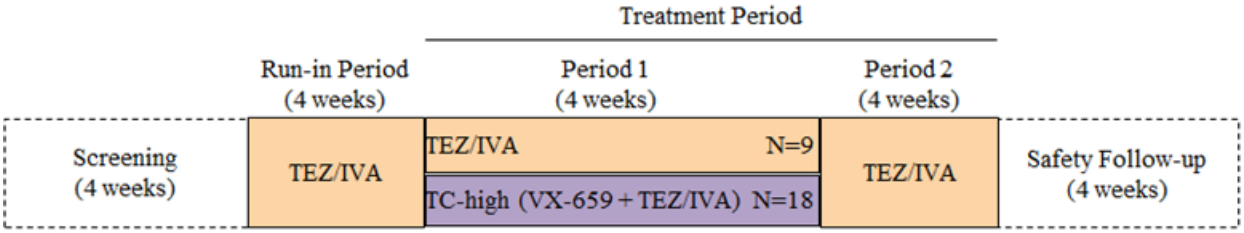
IVA: ivacaftor; q12h: every 12 hours; qd: daily; TC: triple combination; TEZ: tezacaftor
[a] In Part 2, all subjects will also receive TEZ 100 mg qd/IVA 150 mg q12h during the Run-in Period

Figure 6-1 Schematic of Study Design

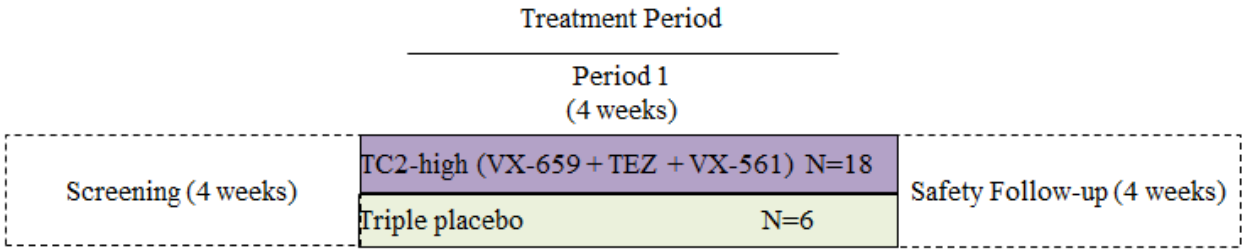
Part 1: Subjects With F/MF Genotypes



Part 2: Subjects With F/F Genotype



Part 3: Subjects with F/MF Genotypes (optional)



F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a minimal *CFTR* function mutation that is not expected to respond to TEZ, IVA, or TEZ/IVA; IVA: ivacaftor; N: number of subjects; TEZ: tezacaftor; TC: triple combination

Note: To maintain the blind, matching placebo tablets will be administered, as applicable, so that all subjects receive the same number of tablets within a given dosing period.

6.2 Sample Size and Power

6.2.1 Primary Objectives

The primary objectives of the study are the evaluation of safety and tolerability, and efficacy of VX-659 in TC with TEZ and either IVA or VX-561. The sample size calculations described below are deemed adequate to evaluate the objectives of the study, based on clinical and statistical considerations.

6.2.1.1 Safety and Tolerability

The primary safety endpoint is the incidence of AEs. Approximately 105 subjects will be randomized in the study with approximately 81 subjects receiving VX-659 in TC. The sample size for each treatment group will provide sufficient data for a descriptive analysis of AEs.

6.2.1.2 Efficacy

The primary efficacy endpoint is the absolute change from baseline in $ppFEV_1$ through the Day 29 Visit in all parts. A sample size of 18 subjects per treatment group provides at least 90% power to detect a mean within-group change of 7 percentage points.

6.2.2 Secondary Objectives

A secondary objective of the study is the evaluation of the PD effect of VX-659 in TC with TEZ and either IVA or VX-561.

The absolute change from baseline through the Day 29 Visit in sweat chloride concentrations is a secondary endpoint used to evaluate the PD objective of the study. In Part 1, a test for a decreasing dose-response trend between placebo and the TC dose groups will be performed using a multiple comparisons procedure (MCP). The procedure consists of testing the null hypothesis of the lack of a decreasing dose-response trend versus a decreasing trend using the 1-sided maximum *t*-statistic that controls the type I error at alpha = 5%. The procedure requires a family of candidate dose-response models to be prespecified, that covers the range of plausible and diverse dose-response profiles.

6.3 Randomization

For all parts, randomization will be stratified by $ppFEV_1$ values (<70 vs ≥70).

For subjects in Part 1 and Part 3, the spirometry assessment used for stratification must be performed at least 14 days after the last dose of any previous CFTR modulator treatment. Therefore, subjects being treated with 1 or more CFTR modulators (investigational or approved) within 14 days of the Screening Visit must have a separate Stratification Visit at least 14 days after the subject's last CFTR modulator dose. For subjects not being treated with any CFTR modulators within 14 days of the Screening Visit, the Screening Visit spirometry assessment can be used for stratification.

For subjects in Part 2, the $ppFEV_1$ assessment for stratification of randomization will be done at the Day -14 Visit. See Section 9.3.1 of the protocol.

Randomization will occur before the first dose of VX-659/control and may be done on either Day -1 or the Day 1 Visit, after all inclusion and exclusion criteria have been satisfied and the criteria for entry into the Treatment Period have been confirmed (see Section 9.1.4 of the protocol).

For Part 2, subjects who prematurely discontinue TEZ/IVA during the Run-in Period will not be randomized or participate in the Treatment Period, unless they rescreen and complete a 4-week Run-in Period (Section 9.1.2 of the protocol).

6.4 Blinding and Unblinding

6.4.1 Blinding

This will be a double-blind study.

6.4.2 Blinding

All subjects, site personnel (including the investigator, the site monitor, and the study team), and the Vertex study team will be blinded to the treatment codes 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 her 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 IWRS Manager
- Vertex Clinical Supply Chain
- Independent Data Monitoring Committee (IDMC)
- Vendor performing the interim analyses (IAs) and preparing the unblinded analysis for the ongoing reviews of efficacy and safety data, and the IDMC

- Bioanalytical contract research organization (CRO) analyzing PK samples and Vertex Bioanalytical personnel who are not members of the study team may review raw data from Bioanalytical CRO.
- Vertex Modeling and Simulation personnel or vendor conducting the population PK and PK/PD analyses
- Vertex medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time

Blinding of Sweat Chloride and Spirometry Results:

- The Vertex study team will not have access to sweat chloride or spirometry results after a subject receives the first dose of study drug on the Day 1 Visit until after the data are unblinded for full review per Section 12.3.6.1 of the protocol.
- Sites, subjects, and their parents/caregivers/companions should not be informed of a subject's study-related sweat chloride results until after the subject's last study visit, even if the subject prematurely discontinues treatment.
- Subjects and their parents/caregivers/companions should not be informed of the subject's study-related spirometry results until after the subject's last study visit, even if the subject prematurely discontinues treatment.

6.4.3 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 Individual Subject Treatment Assignments by Investigator for Medical Emergencies or Urgent Clinical Situations

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 will 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 it 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 will 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 will 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 the sponsor (Vertex), CRO, or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS or designee, per Section 13.1.2 of the protocol.

Unblinding of Individual Subject Treatment Assignments by Vertex GPS or Designee for SAEs or Safety Concerns

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

Unblinded Reviews of Data by Vertex for Administrative Purposes (Planning, Decision-making, and Regulatory Submission)

A limited Vertex team will be unblinded and have access to safety, efficacy, and PD data for the purpose of conducting ongoing reviews of safety and efficacy data for planning and enabling clinical development. Members of the limited unblinded Vertex team will not be part of the Vertex study team and will not be involved in or influence the conduct of the study.

Unblinding: Interim Analysis Results

Interim analyses (IAs) may be conducted for any part of the study after at least 50% of subjects in the part have completed the Day 15 Visit (see Section 12.3.6.1 of the protocol). Each IA will only include data for a single part of the study. The results of these analyses will be reviewed by a limited Vertex team. When an IA is performed after all subjects in a part have completed the Safety Follow-up Visit, results from that part will be unblinded for full review by the Vertex study team.

7 ANALYSIS SETS

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

7.1 All Subjects Set

The **All Subjects Set** will include all subjects who were randomized or received at least 1 dose of study drug. This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

7.2 Full Analysis Set

The **Full Analysis Set** (FAS) will be defined as all randomized subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug in Period 1. The FAS will be used to summarize subject demographics and baseline characteristics, and for all PD and efficacy analyses, unless specified otherwise. Subjects will be analyzed according to the treatment they were randomized to.

7.3 Safety Set

7.3.1 Parts 1 and 3

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

If a subject received at least 1 dose of a higher TC treatment group, the subject will be analyzed in the higher dose TC treatment group (in increasing priority order of triple placebo, TC-low, TC-mid, and TC-high or TC2-high).

7.3.2 Part 2

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

The **Safety Set for the Treatment Period** will include all subjects who received at least 1 dose of study drug in Period 1 of the Treatment Period. This Safety Set will be used for all safety analyses for the Treatment Period, unless specified otherwise.

If a subject received at least 1 dose of a higher TC treatment group, the subject will be analyzed in the higher dose TC treatment group (in increasing priority order of TEZ/IVA and TC-high).

Note: The safety analysis will focus on the Safety Set for the Treatment Period only, unless otherwise specified.

8 STATISTICAL ANALYSIS

8.1 General Considerations

The analysis will be performed for each part, and presented by treatment group and overall, for the Treatment Period, unless specified otherwise. The treatment groups are defined as follows:

- Part 1: *F508del*/MF genotype group
    - Placebo, TC-low, TC-mid, and TC-high.
- Part 2: *F508del*/*F508del* genotype group
    - TEZ/IVA and TC-high.
- Part 3: *F508del*/MF genotype group
    - Placebo and TC2-high.

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

All individual subject data for those randomized or dosed with any amount of study drug will be presented in data listings.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, standard error (SE), median, minimum value (min), and maximum value (max). SE may not be reported for safety summary tables.

Categorical variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place.

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

Absolute change from baseline will be calculated as postbaseline value – baseline value.

Relative change from baseline will be calculated as (postbaseline value – baseline value)/baseline value.

Treatment-emergent (TE) period for Parts 1 and 3 will be from the first dose date of study drug in the Treatment Period until 28 days after the last dose date of study drug or end of study date (based on end of study visit in CRFs), whichever occurs first.

For Part 2, the TE period will be defined separately for the Run-In Period, and the Treatment Period:

The TE period for the Run-in Period will be from the first dose date of study drug in the Run-in Period to: (1) the first dose date of study drug in the Treatment Period for subjects who complete the Run-in Period and continue to the Treatment Period, or (2) 28 days after the last dose date of study drug in the Run-in Period or end of study date (based on end of study visit in CRFs), whichever occurs first, for subjects who do not continue to the Treatment Period (e.g., subjects who do not meet the criteria to enter the Treatment Period and re-enter Study 661-110). The TE period for the Treatment Period will be from first dose date of study drug in the Treatment Period to 28 days after the last dose date of study drug or end of study date (based on end of study visit in CRFs), whichever occurs first.

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

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

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

Spirometry ($ppFEV_1$) will be used for both efficacy and safety purposes. For efficacy analysis, the assessments will follow the visit windowing rules for efficacy. For safety analysis, the assessments at pre-dose and 5 hours postdose on nominal days 1 and 15 will be used.

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

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

Multiplicity: There will be no multiplicity adjustment for performing multiple hypothesis tests, unless specified otherwise.

8.2 Background Characteristics

8.2.1 Subject Disposition

For the Treatment Period in all Parts, subject disposition will be summarized as described below.

The number of subjects in the following categories will be summarized by treatment group and overall, for Parts 1 and 3:

- All Subjects Set (randomized or dosed)
- Randomized
- Safety Set
- Randomized but not dosed in Period 1 of the Treatment Period
- Full Analysis Set (FAS)

The number of subjects in the following categories will be summarized by treatment group and overall for Part 2:

- Randomized or dosed in the Period 1 of the Treatment Period
- Randomized
- Safety Set for the Treatment Period
- Randomized but not dosed in Period 1 of the Treatment Period
- Full Analysis Set (FAS)

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

- Completed study drug treatment (separately by Periods 1 and 2 for both Part 1 and Part 2)
- Prematurely discontinued treatment and the reason for discontinuation (i.e., discontinued all study drugs) (separately by Periods 1 and 2 for both Part 1 and Part 2)
- Completed study (i.e., completed Safety Follow-up Visit or completed all study drugs and re-entered Study 661-110 without Safety Follow-up per protocol)
- Prematurely discontinued the study and the reason for discontinuation

For the Run-in Period in Part 2, a separate disposition table will be provided with the following categories:

- Safety Set for the Run-in Period
- Enrolled but not dosed in the Run-in Period
- Completed treatment in the Run-in Period (i.e., completed randomization)
- Prematurely discontinued treatment during the Run-in Period and the reason for treatment discontinuation (i.e., discontinued all study drugs in the Run-in Period)

- Prematurely discontinued the study during the Run-in Period and the reason for study discontinuation

A listing will be provided by part, for subjects who discontinued treatment (including the Run-in Period in Part 2) or who discontinued study with reasons for discontinuation. A randomization listing of subjects will also be provided, by part.

8.2.2 Demographics and Baseline Characteristics

Demographics, medical history and baseline characteristics will be summarized based on the FAS, and presented by treatment group and overall, for each part, as applicable.

Demographic data will include the following:

- Age at baseline (in years)
- Sex (female and male)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other)

Baseline characteristics will include the following:

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

Stratification categories will include the following:

- $ppFEV_1$ at stratification (< 70 and ≥ 70)

  For Parts 1 and 3, $ppFEV_1$ stratification (<70 versus ≥70) will be performed at Stratification Visit for subjects being treated with 1 or more CFTR modulators (investigational or approved) within 14 days of the Screening Visit. For subjects not being treated with any CFTR modulators within 14 days of the Screening Visit, the Screening Visit spirometry assessment can be used for stratification.
  For subjects in Part 2, the $ppFEV_1$ assessment for stratification of randomization will be done at the Day -14 Visit.

Disease characteristics will include the following:

- $ppFEV_1$ at baseline (<40, ≥ 40 to <70, ≥70 to ≤90, >90)
- $ppFEV_1$ at baseline (continuous)
- Sweat Chloride at baseline (continuous)
- FEV_1 (L) at baseline (continuous)
- CFQ-R Respiratory Symptoms domain at baseline (continuous)
- Prior use of dornase alfa before first dose of study drug in the Treatment Period (Yes, No)

- Prior use of inhaled antibiotic before first dose of study drug in the Treatment Period(Yes, No)
- Prior use of any bronchodilator before first dose of study drug in the Treatment Period (Yes, No)
- Prior use of any inhaled bronchodilator before first dose of study drug in the Treatment Period (Yes, No)
- Prior use of any inhaled hypertonic saline before first dose of study drug in the Treatment Period (Yes, No)
- Prior use of any inhaled corticosteroids before first dose of study drug in the Treatment Period (Yes, No)
- Infection with *Pseudomonas aeruginosa* at baseline (Positive, Negative)

A summary of medical history will be provided by MedDRA System Organ Class (SOC) and Preferred Term (PT) for the FAS. In addition, the number of subjects reported to have had positive cultures for respiratory pathogens in 2 years prior to screening will be summarized for the FAS. Further, the CFTR genotype for each subject will be provided in an individual subject data listing.

8.2.3 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHODDE) and categorized as follows:

For Parts 1 and 3:

Prior medication: any medication that started before the first dose date of study drug, regardless of when the medication ended.

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

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

For Part 2:

Prior medication: any medication that started before the first dose date of study drug in the Run-in Period, regardless of when the medication ended.

Concomitant medication during the Run-in Period: medication continued or newly received on or after the first dose date of study drug during the Run-in Period through the end of the TE period for the Run-in Period.

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

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

A given medication may be classified as follows: prior, concomitant, post-treatment, both prior and concomitant, both concomitant and post-treatment, or prior, concomitant, and

post-treatment. In Part 2, concomitant may be concomitant during the Run-in Period, or concomitant during the Treatment Period, or both.

If a medication has a completely missing or partially missing start/stop date and it cannot be determined whether it was taken before the first dose date of study drug, concomitantly, or after the TE period, it will be classified as prior, concomitant, and post-treatment.

Prior medications and concomitant medications will be summarized descriptively using frequency tables by preferred name.

Summaries of medications will be based on the FAS, and presented by treatment group and overall for each part.

Post-treatment medications will be listed by subject.

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

8.2.4 Study Drug Exposure

Study drug exposure (in days) will be calculated as: last dose date of study drug – first dose date of study drug + 1 day, regardless of study drug interruption, and will be summarized descriptively. Study drug exposure will be summarized for the overall study drug period, which includes the Treatment Period for Parts 1 and 3, and the Run-in Period and the Treatment Period for Part 2. Further, study drug exposure for the Treatment Period in Part 2 will also be summarized descriptively.

Study drug exposure (in weeks) will be summarized descriptively by the number of subjects (n), mean, SD, SE, median, min, and max. It will also be summarized in categories for Treatment Period: ≤2 weeks, >2- ≤4 weeks, and > 4 weeks (for Parts 1 and 3); and ≤2 weeks, >2- ≤4 weeks, >4 - ≤8 weeks, >8 weeks (for Part 2), using counts and percentages. Additionally, the total study drug exposure, defined as the sum total of the study drug exposure across all subjects (in patient-weeks), will be provided.

Exposure summaries will be based on the Safety Set, and presented by treatment group and overall, for each part. For Part 2, exposure summaries will be based on the Safety Set for the Treatment Period.

8.2.5 Study Drug Compliance

Percentage of tablets taken will be calculated as: 100 × [(total number of tablets dispensed) – (total number of tablets returned)]/(total number of tablets planned to be taken per day × duration of study drug exposure in days). The maximum percentage of tablets taken will be 100%.

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

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

For all parts, study drug compliance and percentage of tablets taken will be summarized for Period 1 in the Treatment Period only.

Percentage of tablets taken and study drug compliance summaries will be based on the FAS, and presented by treatment group and overall, for each part.

8.2.6 Important Protocol Deviations

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

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

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

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

IPDs will be provided in an individual subject data listing for each part. Details of the IPD rules are provided in Appendix D.

8.3 Efficacy Analysis

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

The analysis will include all available measurements through the last scheduled Treatment Period visit including measurements after treatment discontinuation, per the visit windowing rules described in Appendix B.

Except the sensitivity analyses, the post-dose measurements on the same day (e.g. days when spirometry is repeated pre- and post-dose) will not be used for any model-based analyses, but only reported in descriptive safety analyses.

8.3.1 Primary Efficacy Variable

The primary efficacy variable is the absolute change from baseline in $ppFEV_1$ (in percentage units) through Day 29 in each part.

$ppFEV_1$ 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 Quanjer GLI-2012 Regression Equations and Lookup Tables[1], adjusting for age, height, sex and ethnicity. Details are provided in Appendix E.

8.3.1.1 Primary Analysis of the Primary Efficacy Variable

8.3.1.1.1 All Parts: Period 1 in the Treatment Period

The null hypothesis to be tested is that the mean absolute within-group change from baseline in $ppFEV_1$ through Day 29 is zero for VX-659 in TC with TEZ and either IVA or VX-561, for each part, separately. A 2-sided *p*-value of 0.05 or less will be interpreted as sufficient evidence to reject the null hypothesis.

The primary analysis will be performed using a mixed-effects model for repeated measures (MMRM) with change from baseline in $ppFEV_1$ as the dependent variable for each part, separately. For Part 1, the analysis will include 4 treatment groups: placebo, TC-low, TC-mid, and TC-high. For Part 2, the analysis will include 2 treatment groups: placebo + TEZ/IVA, and TC-high (VX-659 + TEZ/IVA). For Part 3, the analysis will include 2 treatment groups: placebo and TC2-high (VX-659+TEZ+VX-561). The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects and subject as a random effect, with the continuous baseline $ppFEV_1$ as a covariate, and will include all data from each treatment group and visit during Period 1 in the analysis. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the F test for fixed effects will be estimated using the Kenward-Roger approximation. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, a reduced compound symmetry covariance structure will be used instead. Conditional on the observed data and covariates, missing $ppFEV_1$ data due to treatment or study discontinuation will be assumed to be missing at random; consequently, no imputation of missing data will be performed.

The adjusted means and 95% confidence intervals (CI) of the average treatment effect through Day 29 for each TC, with a 2-sided *p*-value will be estimated within MMRM using PROC MIXED in SAS, for all within-treatment and between-treatment comparisons, for each part, separately. Contrasts based on the fixed effects in the model, defined at the baseline covariate mean for the combined treatment groups using unique subjects in the FAS who have at least one post-baseline measurement through Day 29, will be used to estimate the average treatment effect across post-baseline visits through Day 29.

Further, the adjusted mean and 95% CI of the treatment difference between each TC group and placebo or TEZ/IVA at each post-baseline visit through Day 29 will be provided along with the corresponding *p*-value, for each part. In addition, the adjusted mean and 95% CI of the within-treatment difference at each post-baseline visit through Day 29 for each treatment group will be provided along with the *p*-value, for each part.

The adjusted mean (with 95% CI) obtained from the MMRM analysis at each post-baseline visit through Day 29 will be plotted by treatment group, for each part. In addition, a waterfall plot showing the subject-level absolute change in $ppFEV_1$ at Day 29 will be presented, by treatment group.

The primary analysis will use pre-dose measurements only. The post-dose measurements on the same day will be used for sensitivity analysis as described in the next section.

In addition, for each part, descriptive analyses of the change from baseline will be performed for all treatment groups by post-baseline visit through the safety follow-up visit.

[redacted]

8.3.2 Analysis of Secondary Efficacy Variables

The secondary efficacy variables include:

- Relative change in ppFEV$_1$ from baseline through the Day 29 Visit

- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline at the Day 29 Visit

8.3.2.1 Relative change in ppFEV$_1$ from baseline through Day 29 (All Parts)

The relative change in ppFEV$_1$ from baseline through the Day 29 Visit is defined in Section 8.1. Analysis of this variable will be based on an MMRM model, similar to the primary analysis of the primary efficacy variable in each part. The tabular presentation of results will also be similar.

8.3.2.2 Absolute change in the CFQ-R respiratory domain score from baseline at Day 29 (All Parts)

The absolute change in the CFQ-R respiratory domain score from baseline at the Day 29 Visit will use the 'Adolescents and Adults' Version for ages 14 and above at baseline, and will be based on the *CFQ-R scaled scores*, as described in Appendix F. Analysis of this variable will be based on an MMRM model, similar to the analysis of the primary efficacy variable in Parts 1, 2 and 3. Sex, the continuous baseline ppFEV$_1$, and the continuous baseline CFQ-R respiratory domain score will be used as covariates in each part.

In Part 2, a supportive analysis will be based on fitting a fully saturated model to the CFQ-R respiratory domain score in the Day 43 and Day 57 Visits during Period 2, using randomized group, visit, and the group-by-visit interaction effect as a fixed effect, and sex, continuous baseline ppFEV1 and continuous baseline CFQ-R respiratory domain score as covariates in the MMRM model. The other aspects of the MMRM model will be similar to that of the primary analysis.

The tabular presentation of results for the average treatment effect across visits will be similar to the primary analysis of the primary efficacy variable. The adjusted mean (with 95% CI) obtained from the model-based analysis at each post-baseline visit in Period 2 will be plotted by group, and combined with the corresponding plot for Period 1.

In addition, for all parts a waterfall plot showing the subject-level absolute change in CFQ-R at Day 29 will be presented, by treatment group.

8.3.2.3 Multiplicity adjustment

There will be no multiplicity adjustment to control the overall type 1 error rate for secondary efficacy variables.

8.3.3 Analysis of Other Efficacy Variables (All Parts)

Other efficacy variables include:

- Absolute change in CFQ-R non-respiratory domain scores from baseline at the Day 29 Visit

Only descriptive analyses will be performed.

8.3.3.1 Absolute change in CFQ-R non-respiratory domain scores from baseline at Day 29 (All Parts)

The Adolescent/Adult version includes the following non-respiratory domains: Body Image, Digestive Symptoms, Eating Problems, Emotional Functioning, Health Perceptions, Physical Functioning, Role Functioning, Social Functioning, Treatment Burden, Vitality, and Weight.

The absolute change in CFQ-R non-respiratory domain scores from baseline at Day 29 will use the 'Adolescents and Adults' Version for ages 14 and above at baseline, and will be based on the *CFQ-R scaled scores*, as described in Appendix F. Descriptive analyses will be performed for all treatment groups by post-baseline visit.

8.3.5 Pharmacodynamic Analysis

The sweat chloride measurement for a given visit will be calculated as the mean of the non-missing sweat chloride measurements obtained on the left and right arms at that visit. If one of the two arm measurements at a time point is missing, the other will be used as the mean. A volume ≥15 μL is required for an accurate determination of sweat chloride. Any results reported as having volume <15 μL will be considered missing. Any sweat chloride values reported as <10 mmol/L or >160 mmol/L will be considered missing.

The analysis of the PD effect of VX-659 in combination with TEZ and either IVA or VX-561 in Parts 1, 2, and 3 on sweat chloride concentrations will be described in this section.

Descriptive analyses of the change from baseline will also be performed for all treatment groups by post-baseline visit.

8.3.5.1 Primary Analysis of the Dose Response trend of absolute change in sweat chloride from baseline through the Day 29 Visit (Part 1)

The null hypothesis to be tested is that the dose response of the mean absolute change from baseline through the Day 29 Visit for sweat chloride is not decreasing between placebo and the 3 dose levels of VX-659 with TEZ/IVA in Part 1. The test will be performed using the MCP procedure with the pre-specified contrasts provided in Section 6.2.2, within a linear MMRM framework using PROC GLIMMIX in SAS. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects and subject as a random effect, with continuous baseline $ppFEV_1$ and continuous baseline sweat chloride as covariates, and will include all data from all treatment groups and visits through the Day 29 Visit for analysis. The dose response test will be based on the 1-sided maximum *t*-statistic of the individual *t*-statistics for the multiple pre-specified contrasts at alpha = 5%, based on the treatment group means through the Day 29 Visit, using an unstructured covariance structure for the within-subject errors. If the model estimation does not converge, a reduced compound symmetry covariance structure will be used instead.

The tabular presentation of results for the average treatment effect across visits will be similar to the primary analysis of the primary efficacy variable for all parts. The corresponding *p*-value for the decreasing dose response trend will be provided.

In addition, descriptive analyses of the change from baseline will be performed for all treatment groups by post-baseline visit.

8.3.5.2 Absolute Change in Sweat Chloride from Baseline through the Day 29 Visit (All Parts)

The analysis of the absolute change in sweat chloride from baseline through the Day 29 Visit will be based on an MMRM model similar to the analysis of the primary efficacy variable, with the continuous baseline $ppFEV_1$ and continuous baseline sweat chloride as covariates. The presentation of results will also be similar.

The adjusted mean (with 95% CI) obtained from the MMRM analysis at each post-baseline visit through the Day 29 Visit in the Period 1 will be plotted by treatment group, for each part.

A waterfall plot showing the subject-level absolute change in sweat chloride at Day 29 will be presented, by treatment group for each part.

In addition, for each part, descriptive analyses of the change from baseline will be performed for all treatment groups by post-baseline visit.

[redacted]

8.4 Safety Analysis

For Parts 1 and 3, all safety analyses will be based on data from the TE Period for all subjects in the Safety Set. For Part 2, all safety analyses will be based on the TE Period for the Treatment Period for all subjects in the corresponding Safety Set for the Treatment Period.

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

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., hematology, serum chemistry, coagulation, and urinalysis)
- ECGs
- Vital signs
- Pulse oximetry
- Spirometry

All safety data will be summarized by treatment group and overall, for each part.

8.4.1 Adverse Events

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

For Parts 1 and 3:

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

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

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

For Part 2:

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

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

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

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

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

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

AE summary tables will be presented for TEAEs only, for the TE period for Parts 1 and 3, or the TE period for the Treatment Period in Part 2, by treatment group and overall, for each part respectively, as applicable, for the following:

- Number of TEAEs (total number of TEAEs only)
- Subjects with any TEAEs
- Subjects with TEAEs by Strongest Relationship
- Subjects with TEAEs by Maximum Severity
- Subjects with TEAEs Leading to Study Drug Discontinuation (Discontinuation of all study drug)
- Subjects with TEAEs Leading to Study Drug Interruption (Interruption of all study drug)
- Subjects with Serious TEAEs
- Subjects with TEAE Leading to Death

Summaries will be presented by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and

percentages of subjects, subjects with multiple occurrences of the same adverse event or a continuing adverse event will be counted once, and only the maximum severity level will be presented in the severity summaries, and the strongest relationship level in the relationship summaries.

All AEs, including pre-treatment AEs, TEAEs for all applicable periods, and post-treatment AEs, will be presented in an individual subject data listing based on the All Subjects Set. Further, subjects who enrolled from Study 661-110 will be identified from the subject ID in the listing.

8.4.2 Clinical Laboratory

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

The number and percentage of subjects meeting at least 1 threshold analysis criterion event, during the TE period for Parts 1 and 3, or the TE period for Treatment Period for Part 2, will be summarized by treatment group and overall for each part. The threshold analysis criterion shift from baseline will also be summarized for selected laboratory parameters. The threshold analysis criteria are provided in Appendix H.

For select LFT laboratory test (alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALP], and total bilirubin), a scatter plot of the maximum treatment-emergent value versus the baseline value corresponding to ×ULN (upper limit of normal) will be presented. Further, a scatter plot of the maximum treatment-emergent value of ALT and AST, separately, versus the maximum treatment-emergent value of total bilirubin corresponding to ×ULN will also be presented by treatment group, for each part.

Results of abnormal urinalysis and positive urine/serum pregnancy test will be listed in individual subject data listings only.

In addition, a listing containing individual subject hematology, chemistry, and coagulation values outside the normal reference ranges will be provided. This listing will include data from both scheduled and unscheduled visits.

8.4.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided at each scheduled visit and time point, by treatment group, for each part, for the following ECG interval measurements (in ms): RR, PR, QT, and QT corrected for HR (QTcF), QRS duration, and HR (beats per minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE period for Parts 1 and 3, or the TE period for the Treatment Period in Part 2, will be summarized by treatment group and overall, for each part. The threshold analysis criteria are provided in Appendix H.

8.4.4 Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized by treatment group, at each scheduled visit, for each part, as applicable. The following vital signs parameters will be summarized: systolic and diastolic blood

pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE period for Parts 1 and 3, or the TE period for the Treatment Period in Part 2, will be summarized by treatment group and overall, for each part. The threshold analysis criteria are provided in Appendix H.

8.4.5 Pulse Oximetry

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

The number and percentage of subjects with shift changes from baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the TE Period for Parts 1 and 3, or the TE period for the Treatment Period in Part 2, will be summarized by treatment group and overall, for each part.

8.4.6 Physical Examination

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

8.4.7 Other Safety Analysis

8.4.7.1 Post-dose Spirometry

A summary of the pre-dose values for $ppFEV_1$ and change from pre-dose value for the post-dose $ppFEV_1$ value at 5 hours post-dose will be presented on nominal visits Day 1 and Day 15, by treatment group, for each part. Further, a box plot of differences (post-dose - pre-dose) will be presented by visit and treatment group, for each part.

9 INTERIM AND IDMC ANALYSES

9.1 Interim Analysis

A separate IA may be performed after all subjects in Part 1, Part 2, and Part 3 have completed the Safety Follow-up Visit. All data from the part will be unblinded after the data from that part are cleaned for analysis and a data cut is performed. The Vertex Study Team will be unblinded to the interim analysis results.

In addition, IAs may be performed for each part after 50% of subjects in the part have completed the Day 15 Visit. These results will be reviewed by a limited Vertex team.

9.1.1 Summary of the Flow of Data for Interim Analyses

To protect the integrity of the treatment assignment and study data, the following steps for the flow of data will be executed for each interim analysis performed after at least 50% of the subjects have completed the Day 15 visit in each part:

1. The blinded Vertex Biometrics group will prepare the SAS codes, SDTM/ADaM data sets, and blinded outputs (tables, figures and listings) of safety, efficacy and PD data using dummy treatment codes, dummy spirometry data, and dummy sweat chloride data;

2. The IWRS vendor, Bracket, will provide the unblinded treatment codes to the unblinded Vertex Biometrics team, via Kiteworks;
3. Biomedical Systems (BMS) will provide the unblinded spirometry data to unblinded Vertex Biometrics team, via Kiteworks; ICON Central Labs will provide the unblinded sweat chloride data to unblinded Vertex Biometrics team, via Kiteworks;
4. An unblinded Vertex Biometrics group will generate the unblinded outputs and provide them directly to the limited Vertex team for their review.

9.2 IDMC Analysis

The IDMC's objectives and operational details were defined in a separate document (IDMC Charter) which was finalized before the first subject was screened in the study. The IDMC's planned safety reviews of study data are outlined in the IDMC Charter and IDMC Statistical Analysis Plan. Further, planned ongoing reviews of key study data by the limited Vertex team are also described in the IDMC Statistical Analysis Plan.

10 REFERENCES

[1]Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall G, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.

11 LIST OF APPENDICES

Appendix A: Schedule of Assessments

Table 11-1 Study VX16-659-101 Part 1 (Subjects with F/MF genotypes): Schedule of Assessments

Event/Assessment[a]	Screening Period		Treatment Period (5 weeks)				ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
			Period 1[c] (4 weeks)			Period 2		
	Screening Visit Days -28 to -1	Stratification Visit[d] Day -27 to -1	Day 1	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 33 Visit[e]		
Informed consent	X							
Randomization[f]			X					
Study drug dosing[g]			Day 1 through Day 33 Visit					
Demographics	X							
Medical history	X							
CFTR genotype[h]	X							
Height[i]	X							
Weight[i]	X		X	X	X		X	X

[a] All assessments will be performed predose, unless noted otherwise. Assessments that are collected predose and postdose will only be collected once if study drug is not administered on the day of the visit (i.e., if subject prematurely discontinued study drug treatment).

[b] If the subject prematurely discontinues study drug treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the decision to discontinue study drug treatment. Subjects who prematurely discontinue treatment will be required to complete the Safety Follow-up Visit. If the ETT Visit occurs 3 or more weeks after the last dose of study drug, the ETT Visit will replace the Safety Follow-up Visit (a separate Safety Follow-up Visit is not required).

[c] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 9.1.4.

[d] The spirometry assessment used for stratification must be performed at least 14 days after the last dose of any previous CFTR modulator treatment. Therefore, subjects being treated with 1 or more CFTR modulators (investigational or approved) within 14 days of the Screening Visit must have a separate Stratification Visit at least 14 days after the subject's last CFTR modulator dose. For subjects not being treated with any CFTR modulators within 14 days of the Screening Visit, the Screening Visit spirometry assessment can be used for stratification.

[e] The Day 33 Visit may occur 3 to 6 days after the actual date of the Day 29 Visit.

[f] Randomization may occur on the previous day (Day -1) after all inclusion and exclusion criteria and criteria for entry into the Treatment Period (see footnote c) have been confirmed.

[g] On days of scheduled visits, the in-clinic dose of study drugs will be given in the morning, at least 6 hours apart from any other scheduled dose and after all predose assessments are complete. The last dose of VX-659 in Part 1 Period 1 will be the morning dose on the Day 29 Visit. The last dose of TEZ/IVA in Part 1 Period 2 will be the morning dose on the Day 33 Visit. Refer to Section 9.7 for details.

[h] *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility (see inclusion criterion 6).

Table 11-1 Study VX16-659-101 Part 1 (Subjects with F/MF genotypes): Schedule of Assessments

Event/Assessment[a]	Screening Period		Treatment Period (5 weeks)				ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
			Period 1[c] (4 weeks)			Period 2		
	Screening Visit Days -28 to -1	Stratification Visit[d] Day -27 to -1	Day 1	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 33 Visit[e]		
Physical examination[j]	Complete		Abbrev.	Abbrev.	Abbrev.		Abbrev.	Complete
Vital signs[k]	X		X	X	X	X	X	X
Pulse oximetry[k]	X		X	X	X	X	X	X
Standard 12-lead ECG[l]	X		X	X	X		X	X
Sweat chloride[m,p]	X		X	X	X	X	X	X
Spirometry[n]	X	X	X	X	X	X	X	X
CFQ-R[o,p]			X	X	X			
Urinalysis[p]	X		X	X	X		X	X
Pregnancy test (females of childbearing potential)	Serum		Urine		Urine		Serum	Serum
FSH[q]	X							

[i] Weight and height will be measured with shoes off.
[j] Complete and abbreviated physical examinations (PEs) are described in Section 11.7.3. Symptom-directed PEs can be done at any time at the discretion of the investigator or healthcare provider.
[k] Vital signs and pulse oximetry will be collected after the subject has been seated for at least 5 minutes.
[l] Standard 12-lead ECGs will be performed after the subject has been rested for at least 5 minutes. On the Day 1 and 15 Visits, ECGs will be collected before dosing and 5 hours (± 1 hour) after dosing. At other visits, ECGs will be collected before dosing (as applicable). ECGs collected on the Day 1 Visit before dosing will be performed in triplicate.
[m] See inclusion criterion 5 for information about the sweat chloride assessment for study eligibility. Sweat chloride assessments should be done at approximately the same time at every study visit during the Treatment Period and follow-up.
[n] At the Screening Visit, spirometry may be done pre- or post-bronchodilator. At other study visits, spirometry will be done pre-bronchodilator, before the in-clinic dose of study drugs, and should be performed at approximately the same time at every visit. On the Day 1 and 15 Visits, spirometry will also be performed 5 hours (± 1 hour) after the in-clinic dose of study drugs.
[o] CFQ-R must be completed before the start of any other assessments scheduled at that visit.
[p] The predose assessment on the Day 1 Visit may be performed on the previous day (Day -1) if randomization has occurred.

Table 11-1 Study VX16-659-101 Part 1 (Subjects with F/MF genotypes): Schedule of Assessments

	Screening Period		Treatment Period (5 weeks)					
			Period 1[c] (4 weeks)			Period 2		
Event/Assessment[a]	**Screening Visit Days -28 to -1**	**Stratification Visit[d] Day -27 to -1**	**Day 1**	**Day 15 (± 2 days)**	**Day 29 (± 2 days)**	**Day 33 Visit[e]**	**ETT Visit[b]**	**Safety Follow-up 28 (± 7) Days After Last Dose**
G6PD activity test[r]	X							
Serum chemistry and hematology[p]	X		X	X	X	X	X	X
Coagulation[p]	X		X	X	X		X	X
PK sampling[s]			X	X	X	X	X	
[redacted]								
AEs, medications[u], treatments, and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit							

[q] FSH will be measured for any potential postmenopausal female subjects with at least 12 months of continuous spontaneous amenorrhea.
[r] Blood samples will be collected for the G6PD activity test.
[s] Blood samples will be collected for PK analysis of study drugs and metabolites. On the Day 1 Visit, samples will be collected before (0 hours) and 1, 2, 4, and 6 hours after the in-clinic dose. On the Day 15 Visit, samples will be collected before (0 hours) and 1, 2, 4, 6, and 8 hours after the in-clinic dose. On the Day 29 and Day 33 Visits, a single sample will be collected before the in-clinic dose. At the ETT Visit, a single sample will be collected.
[redacted]
[u] Refer to Section 9.5 for details.

Table 11-2 Study VX16-659-101 Part 2 (Subjects with F/F genotype): Schedule of Assessments

	Screening Period	Run-in (4 weeks)		Treatment Period (8 weeks)					ETT Visit[b]	Safety Follow-up
				Period 1 (4 weeks)[d]			Period 2 (4 weeks)			
Event/Assessment[a]	Screening Visit Days -56 to -29	Day -28 (± 1 day)	Day -14 (Days -15 to -3)	Day 1	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	Day 57 (± 3 days)		28 (± 7) Days After Last Dose[c]
Informed consent	X									
Randomization[e]				X						
Study drug dosing[f]		Day -28 to Day -1		Day 1 to 29			Day 29 to 57			
Demographics	X									
Medical history	X									
CFTR genotype[g]	X									
Height[h]	X									
Weight[h]	X	X		X	X	X	X	X	X	X
Physical examination[i]	Complete	Complete	Abbrev.	Abbrev.	Abbrev.	Abbrev.		Abbrev.	Abbrev.	Complete
Vital signs[j]	X	X		X	X	X	X	X	X	X

[a] All assessments will be performed predose, unless noted otherwise. Assessments that are collected predose and postdose will only be collected once if study drug is not administered on the day of the visit (i.e., if subject prematurely discontinued study drug treatment).

[b] If the subject prematurely discontinues study drug treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the decision to discontinue study drug treatment. Subjects who prematurely discontinue treatment will be required to complete the Safety Follow-up Visit. If the ETT Visit occurs 3 or more weeks after the last dose of study drug, the ETT Visit will replace the Safety Follow-up Visit (a separate Safety Follow-up Visit is not required).

[c] Part 2 subjects who meet criteria specified in Section 9.1.5 will not have a Safety Follow-up Visit.

[d] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 9.1.4.

[e] Randomization may occur on the previous day (Day -1) after all inclusion and exclusion criteria and criteria for entry into the Treatment Period (see footnote d) have been confirmed.

[f] On days of scheduled visits, the in-clinic dose of study drug will be given in the morning, at least 6 hours apart from any other scheduled dose and after all predose assessments are complete. The last dose of VX-659 in Part 2 Period 1 will be the morning dose on the Day 29 Visit. The last dose of TEZ/IVA in Part 2 Period 2 will be the morning dose on the Day 57 Visit. Refer to Section 9.7 for details.

[g] CFTR genotyping will be performed for all subjects. If the screening CFTR genotype result is not received before randomization, a previous CFTR genotype laboratory report may be used to establish eligibility (see inclusion criterion 6).

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

[i] Complete and abbreviated PEs are described in Section 11.7.3. Symptom-directed PEs can be done at any time at the discretion of the investigator or healthcare provider.

Table 11-2 Study VX16-659-101 Part 2 (Subjects with F/F genotype): Schedule of Assessments

Event/Assessment[a]	Screening Period	Run-in (4 weeks)		Treatment Period (8 weeks)					ETT Visit[b]	Safety Follow-up
				Period 1 (4 weeks)[d]			Period 2 (4 weeks)			
	Screening Visit Days -56 to -29	Day -28 (± 1 day)	Day -14 (Days -15 to -3)	Day 1	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	Day 57 (± 3 days)		28 (± 7) Days After Last Dose[c]
Pulse oximetry[j]	X	X		X	X	X	X	X	X	X
Standard 12-lead ECG[k]	X	X		X	X	X	X	X	X	X
Sweat chloride[l,o]	X		X	X	X	X	X	X	X	
Spirometry[m]	X		X	X	X	X	X	X	X	X
CFQ-R[n,o]				X	X	X	X	X		
Urinalysis[o]	X	X		X	X	X	X	X	X	X
Pregnancy test (all females of childbearing potential)	Serum	Urine		Urine		Urine		Urine	Serum	Serum
FSH[p]	X									
G6PD activity test[q]	X									
Serum chemistry and hematology[o]	X	X		X	X	X	X	X	X	X
Coagulation[o]	X	X		X	X	X			X	X

[j] Vital signs and pulse oximetry will be collected after the subject has been seated for at least 5 minutes.

[k] Standard 12-lead ECGs will be performed after the subject has been rested for at least 5 minutes. On Day 1 and 15 Visits, ECGs will be collected before dosing and 5 hours (± 1 hour) after dosing. At other visits, ECGs will be collected before dosing (as applicable). ECGs collected on the Day 1 Visit before dosing will be performed in triplicate.

[l] See inclusion criterion 5 for information about the sweat chloride assessment for study eligibility. Sweat chloride assessments should be done at approximately the same time at every study visit during the Treatment Period and follow-up.

[m] The ppFEV1 assessment for stratification of randomization will be done at the Day -14 Visit. See Section 9.3.1. At the Screening Visit, spirometry may be done pre- or post-bronchodilator. At other study visits, spirometry will be done pre-bronchodilator, before the in-clinic dose of study drugs, and should be performed at approximately the same time at every visit. On the Day 1 and 15 Visits, spirometry will also be performed 5 hours (± 1 hour) after the in-clinic dose of study drugs.

[n] CFQ-R must be completed before the start of any other assessments scheduled at that visit.

[o] The predose assessment on the Day 1 Visit may be performed on the previous day (Day -1) if randomization has occurred.

[p] FSH will be measured for any suspected postmenopausal female subjects with at least 12 months of continuous spontaneous amenorrhea.

[q] Blood samples will be collected for the G6PD activity test.

Table 11-2 Study VX16-659-101 Part 2 (Subjects with F/F genotype): Schedule of Assessments

	Screening Period	Run-in (4 weeks)		Treatment Period (8 weeks)						Safety Follow-up
				Period 1 (4 weeks)[d]			Period 2 (4 weeks)			
Event/Assessment[a]	**Screening Visit Days -56 to -29**	**Day -28 (± 1 day)**	**Day -14 (Days -15 to -3)**	**Day 1**	**Day 15 (± 2 days)**	**Day 29 (± 2 days)**	**Day 43 (± 3 days)**	**Day 57 (± 3 days)**	**ETT Visit[b]**	**28 (± 7) Days After Last Dose[c]**
PK sampling[r]				X	X	X	X		X	
[redacted]										
AEs, medications , treatments, and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit									

[r] Blood samples will be collected for PK analysis of study drugs and metabolites. On the Day 1 Visit, samples will be collected before (0 hours) and 1, 2, 4, and 6 hours after the in-clinic dose. On the Day 15 Visit, samples will be collected before (0 hours) and 1, 2, 4, 6, and 8 hours after the in-clinic dose. On the Day 29 and 43 Visits, a single sample will be collected before the in-clinic dose. At the ETT Visit, a single sample will be collected.

[redacted]

Refer to Section 9.5 for details.

Table 11-3 Study VX16-659-101 Part 3 (Subjects with F/MF genotypes): Schedule of Assessments

Event/Assessment[a]	Screening Period		Treatment Period (4 weeks)			ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
			Period 1[c] (4 weeks)				
	Screening Visit Days -28 to -1	Stratification Visit[d] Days -27 to-3	Day 1	Day 15 (± 2 days)	Day 29 (± 2 days)		
Informed consent	X						
Randomization[e]			X				
Study drug dosing[f]			Day 1 through Day 29 Visit				
Demographics	X						
Medical history	X						
CFTR genotype[g]	X						
Height[h]	X						
Weight[h]	X		X	X	X	X	X

[a] All assessments will be performed predose, unless noted otherwise. Assessments that are collected predose and postdose will only be collected once if study drug is not administered on the day of the visit (i.e., if subject prematurely discontinued study drug treatment).

[b] If the subject prematurely discontinues study drug treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the decision to discontinue study drug treatment. Subjects who prematurely discontinue treatment will be required to complete the Safety Follow-up Visit. If the ETT Visit occurs 3 or more weeks after the last dose of study drug, the ETT Visit will replace the Safety Follow-up Visit (a separate Safety Follow-up Visit is not required).

[c] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 9.1.4.

[d] The spirometry assessment used for stratification must be performed at least 14 days after the last dose of any previous CFTR modulator treatment. Therefore, subjects being treated with 1 or more CFTR modulators (investigational or approved) within 14 days of the Screening Visit must have a separate Stratification Visit at least 14 days after the subject's last CFTR modulator dose. For subjects not being treated with any CFTR modulators within 14 days of the Screening Visit, the Screening Visit spirometry assessment can be used for stratification.

[e] Randomization may occur on the previous day (Day -1) after all inclusion and exclusion criteria and criteria for entry into the Treatment Period (see footnote c) have been confirmed.

[f] On days of scheduled visits, the in-clinic dose of study drugs will be given in the morning, at least 6 hours apart from any other scheduled dose and after all predose assessments are complete. The last dose of VX-659 and TEZ/VX-561 in Part 3 Period 1 will be the morning dose on the Day 29 Visit. Refer to Section 9.7 for details.

[g] *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility (see inclusion criterion 6).

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

Table 11-3 Study VX16-659-101 Part 3 (Subjects with F/MF genotypes): Schedule of Assessments

Event/Assessment[a]	Screening Period		Treatment Period (4 weeks)			ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
			Period 1[c] (4 weeks)				
	Screening Visit Days -28 to -1	Stratification Visit[d] Days -27 to-3	Day 1	Day 15 (± 2 days)	Day 29 (± 2 days)		
Physical examination[i]	Complete		Abbrev.	Abbrev.	Abbrev.	Abbrev.	Complete
Vital signs[j]	X		X	X	X	X	X
Pulse oximetry[j]	X		X	X	X	X	X
Standard 12-lead ECG[k]	X		X	X	X	X	X
Sweat chloride[l,o]	X		X	X	X	X	X
Spirometry[m]	X	X	X	X	X	X	X
CFQ-R[n,o]			X	X	X		
Urinalysis[o]	X		X	X	X	X	X
Pregnancy test (females of childbearing potential)	Serum		Urine		Urine	Serum	Serum
FSH[p]	X						

[i] Complete and abbreviated physical examinations (PEs) are described in Section 11.7.3. Symptom-directed PEs can be done at any time at the discretion of the investigator or healthcare provider.

[j] Vital signs and pulse oximetry will be collected after the subject has been seated for at least 5 minutes.

[k] Standard 12-lead ECGs will be performed after the subject has been rested for at least 5 minutes. On the Day 1 and 15 Visits, ECGs will be collected before dosing and 5 hours (± 1 hour) after dosing. At other visits, ECGs will be collected before dosing (as applicable). ECGs collected on the Day 1 Visit before dosing will be performed in triplicate.

[l] See inclusion criterion 5 for information about the sweat chloride assessment for study eligibility. Sweat chloride assessments should be done at approximately the same time at every study visit during the Treatment Period and follow-up.

[m] At the Screening Visit, spirometry may be done pre- or post-bronchodilator. At other study visits, spirometry will be done pre-bronchodilator, before the in-clinic dose of study drugs, and should be performed at approximately the same time at every visit. On the Day 1 and 15 Visits, spirometry will also be performed 5 hours (± 1 hour) after the in-clinic dose of study drugs.

[n] CFQ-R must be completed before the start of any other assessments scheduled at that visit.

[o] The predose assessment on the Day 1 Visit may be performed on the previous day (Day -1) if randomization has occurred.

[p] FSH will be measured for any potential postmenopausal female subjects with at least 12 months of continuous spontaneous amenorrhea.

Table 11-3 Study VX16-659-101 Part 3 (Subjects with F/MF genotypes): Schedule of Assessments

Event/Assessment[a]	Screening Period		Treatment Period (4 weeks)			ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
			Period 1[c] (4 weeks)				
	Screening Visit Days -28 to -1	Stratification Visit[d] Days -27 to-3	Day 1	Day 15 (± 2 days)	Day 29 (± 2 days)		
G6PD activity test[q]	X						
Serum chemistry and hematology[o]	X		X	X	X	X	X
Coagulation[o]	X		X	X	X	X	X
PK sampling[r]			X	X	X	X	
[redacted]							
AEs, medications[t], treatments, and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit						

[q] Blood samples will be collected for the G6PD activity test.

[r] Blood samples will be collected for PK analysis of study drugs and metabolites. On the Day 1 Visit, samples will be collected before (0 hours) and 1, 2, 4, and 6 hours after the in-clinic dose. On the Day 15 Visit, samples will be collected before (0 hours) and 1, 2, 4, 6, and 8 hours after the in-clinic dose. On the Day 29 Visit, a single sample will be collected before the in-clinic dose. At the ETT Visit, a single sample will be collected.

[redacted]

Refer to Section 9.5 for details.

Appendix B: Analysis Visit Windows for Safety and Efficacy Assessments

Table 11-4 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)
Safety Assessment (Part 1)			
Serum Chemistry Hematology Vital Signs (excluding Weight)	Day 1 (Baseline) Day 15 Day 29 Day 33 Safety Follow-up	1 15 29 33 61	≤1 Pre-dose [1, 22] Use nominal visit, otherwise use (22, 31] Use nominal visit, otherwise use (31, 47] Use nominal visit
Coagulation Vital Signs (Weight only)	Day 1 (Baseline) Day 15 Day 29 Safety Follow-up	1 15 29 61	≤1 Pre-dose [1, 22] (22,45] Use nominal visit
Standard 12-lead ECG	Day 1 (Baseline; before dosing) Day 1 (5 hours after dosing) Day 15 (before dosing and 5 hours after dosing) Day 29 Safety Follow-up	1 1 15 29 61	Use nominal visit for all visits
Spirometry	Day 1 (5 hours post dose) Day 15 (5 hours post dose)	1 15	Use nominal visit Use nominal visit
Safety Assessment (Part 2)			
Serum Chemistry Hematology Vital Signs (including Weight)	Day 1 (Baseline) Day 15 Day 29 Day 43 Day 57 Safety Follow-up	1 15 29 43 57 85	≤1 Pre-dose [1,22] (22, 36] (36, 50] (50, 71] Use nominal visit
Coagulation	Day 1 (Baseline) Day 15 Day 29 Safety Follow-up	1 15 29 85	≤1 Pre-dose [1,22] (22, 57] Use nominal visit
Standard 12-lead ECG	Day 1 (Baseline; before dosing) Day 1 (5 hours after dosing) Day 15 (before dosing and 5 hours after dosing) Day 29 Day 43 Day 57 Safety Follow-up	1 1 15 29 43 57 85	Use nominal visit for all visits

Table 11-4 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)
Spirometry	Day 1 (5 hours post dose) Day 15 (5 hours post dose)	1 15	Use nominal visit Use nominal visit
Safety Assessment (Part 3)			
Serum Chemistry Hematology Coagulation Vital Signs (including Weight)	Day 1 (Baseline) Day 15 Day 29 Safety Follow-up	1 15 29 57	≤1 Pre-dose [1,22] (22, 43] Use nominal visit
Standard 12-lead ECG	Day 1 (Baseline; before dosing) Day 1 (5 hours after dosing) Day 15 (before dosing and 5 hours after dosing) Day 29 Safety Follow-up	1 1 15 29 57	Use nominal visit for all visits
Spirometry	Day 1 (5 hours post dose) Day 15 (5 hours post dose)	1 15	Use nominal visit Use nominal visit
Efficacy Assessment (Part 1)			
Spirometry Sweat Chloride	Day 1 (Baseline; before dosing) Day 15 (predose)# Day 29 Day 33 Safety Follow-up	1 15 29 33 61	≤1 Pre-dose [1, 22] Use nominal visit, otherwise use (22, 31] Use nominal visit, otherwise use (31, 47] Use nominal visit
CFQ-R	Day 1 Day 15 Day 29	1 15 29	≤1 [1, 22] (22, 45]
Efficacy Assessment (Part 2)			
Spirometry Sweat Chloride CFQ-R	Day 1 (Baseline; before dosing) Day 15 (predose)# Day 29 Day 43 Day 57 Safety Follow-up (Spirometry only)	1 15 29 43 57 85	≤1 Pre-dose [1,22] (22, 36] (36, 50] (50, 71] Use nominal visit
Efficacy Assessment (Part 3)			
Spirometry Sweat Chloride CFQ-R	Day 1 (Baseline; before dosing) Day 15 (predose)# Day 29 Safety Follow-up (no CFQ-R)	1 15 29 57	≤1 Pre-dose [1,22] (22, 43] Use nominal visit

Notes:
[a] Visit name is used to report data in tables, listings and figures.
[b] Target day time point per protocol is predose, except for ECG and SP measurements.
Postdose of spirometry may be used for imputation

The analysis visit windows will be applied using the following rules for both scheduled and unscheduled visits:

1. If no numerical measurement is available within a visit window, the measurement will be considered

Table 11-4 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)

missing for the visit.

2. If there is more than 1 numerical measurement available within the same visit window, use the following rules:
   a. For **efficacy** parameters: if there are multiple measurements within a visit window, the measurement at the scheduled visit will be used. Otherwise,
      i. If there are no measurements at the scheduled visit, then the measurement closest to the target day will be used; or
      ii. If there are multiple measurements with the same distance to the target day, the latest measurement will be used.
   b. For **safety** parameters: if there are multiple measurements within a visit window,
      i. The measurement closest to the target day will be used; or
      ii. If there are multiple measurements within the same distance from the target day, the latest measurement will be used.
      iii. For tables of extreme lab measurements based on ULN or LLN, convert the lab measurements into ×ULN or ×LLN first, and then select the extreme measurement.

Derived Variables:

1. Age (in years) at first dose date

Obtain age at screening (in days) in yy mm format (e.g., 24 years, 6 months) from screening vital signs page, and add 0.5 month to convert to days.

Obtain screening date from Date of Visit (DOV) page.

Then age (in years) at first dose date = integer part of {[(first dose date-screening date) in days + age at screening (in days)]/365.25}.

Correspondingly, age (in months) at first dose date = integer part of 12*{[(first dose date-screening date) in days + age at screening (in days)]/365.25}.

2. Age (in years) at post-baseline visit (for use in calculation of percent predicted spirometry variables)

Age (in years) at post-baseline visit = [(post-baseline visit date – screening date) in days + age at screening (in days)]/365.25

3. Missing First Dose Date or Last Dose Date

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

If the last dose date is missing at final analysis, use maximum of Early Treatment Termination (ETT) visit date and last study drug administration date from EX SDTM domain (excluding PK dosing dates). When a subject is lost to follow up without ETT, impute the last dose date as the last treatment period visit date.

4. Missing Date for Drug Interruption

If the dates for drug interruption are completely missing or partially missing and it cannot be determined in which period the interruption occurred, then assume the interruption occurred during the Treatment Period (Period 1) for 1 day.

5. Sweat Chloride:

The qualified left arm and right arm SWCL assessments on Day 1 with end date/time for a given arm up to 30 minutes after first dose time will be considered for baseline. If Day 1 value is unavailable or invalid, screening value will qualify as baseline.

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

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

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

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

Table 11-5 Prior, Concomitant, and Post Categorization of a Medication in Parts 1 and 3

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

P: Prior; C: Concomitant; A: Post

Table 11-6 Prior, Concomitant, and Post Categorization of a Medication in Part 2

	Medication Stop Date			
Medication Start Date	**< First Dose Date of Run-in TE Period**	**≥ First Dose Date and ≤ End Date of Run-in TE Period**	**≥ First Dose Date and ≤ End Date of Treatment TE Period**	**> End Date of Treatment TE Period**
< First dose date of Run-in TE period	P	PC1	PC1C2	PC1C2A
≥ First dose date and ≤ End date of Run-in TE Period	-	C1	C1C2	C1C2A
≥ First dose date and ≤ End date of Treatment TE Period	-	-	C2	C2A
> End date of Treatment TE Period	-	-	-	A

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

Appendix D: Important Protocol Deviation Rules

An important protocol deviation (IPD) is any protocol deviation that has the potential to 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.
The rules for identifying important protocol deviations (IPDs) will be finalized prior the database lock. The rules will be developed by the Protocol Deviation Review Team (PDRT) consisting of Clinical Operations Study Lead (COSL), the Medical Monitor (MM), the Primary Clinical Data Manager (PCDM), Clinical Pharmacology lead (CPL), and the Study Biostatistician (SB). This team will review protocol deviations from screening throughout study conduct to develop rules for identifying IPDs.
The protocol deviations that should be considered as potential IPDs include, but are not limited to:

- Subject entered the study despite violation of an inclusion or exclusion criteria
- Subject received the wrong treatment or incorrect doses
- Subject received excluded concomitant medications
- Subject remained in study despite meeting withdrawal criteria

Occurrence of any of these events should be considered as potential IPDs, but the PDRT should categorize them as IPDs only if they have the potential to 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.

The following potential protocol deviations will be identified from the clinical database in addition to those identified through the site deviation log. The team then will review the identified list following the above procedure to categorize if a particular occurrence as below is an important deviation.

Important programmable protocol deviations before the first dose

Stratification error will be detected based on comparing the IWRS stratification with the clinical database.

For Parts 1 and 3, $ppFEV_1$ stratification (<70 versus ≥ 70) will be performed at Stratification Visit for subjects being treated with 1 or more CFTR modulators (investigational or approved) within 14 days of the Screening Visit. For subjects not being treated with any CFTR modulators within 14 days of the Screening Visit, the Screening Visit spirometry assessment can be used for stratification.
For subjects in Part 2, the $ppFEV_1$ assessment for stratification of randomization will be done at the Day -14 Visit.

Important programmable protocol deviations during the Treatment Period

1. Compliance < 80%
2. Use of prohibited medications
3. Actual treatment received is different from the randomized treatment

Appendix E: Details of GLI Equations for Calculating ppFEV$_1$

Percent predicted values will be calculated for parameters of FEV_1, FVC, FEV_1/FVC, and $FEF_{25\%-75\%}$ using the Quanjer GLI-2012 Regression Equations and Lookup Tables.

The regression equations and lookup tables required to implement the Quanjer GLI-2012 predicted values are available in:

Quanjer GLI-2012 Regression Equations and Lookup Tables. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 7 April 2013. Available at:

http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/quanjer-gli-2012-regression-equations-and-lookup-tables.aspx

Accessed Sep 11, 2017.

The instructions and tools on how to implement the Quanjer GLI-2012 equations are:

Implementing GLI-2012 regression equations. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 19 July 2015. Available at:

http://www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools/it-engineers-and-manufacturers.aspx

Accessed Sep 11, 2017.

GLI-2012 - SAS Macro. Sanja Stanojevic. Version 2, 7 April 2013. Available at:

http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/sas-macro.aspx

Accessed Sep 11, 2017.

Data handling rule for spirometry is as follows:

- Input age and height with at least 2 decimal place
- Use height at screening regardless if height is collected at study visit
- For race, map CRF black or AA to black, all other races in CRF (except white) are mapped to 'other'; multiple checks for race in CRF are also mapped to 'other'; white is a reference race in the equations and assumes 0 values for all race coeffiecients in the GLI equations.

Appendix F: Details of CFQ-R Analysis and Scoring Manual

The CFQ-R is a valid CF-specific instrument that measures quality-of-life domains. This study uses CFQ-R for Adolescents and Adult (subjects 14 years and older) in this study. 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 domains; all the other 49 questions are scored 1, 2, 3, or 4.

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. In each domain, in cases where individual questions were skipped, the missing scores are imputed with the mean score of the non-missing questions for that domain.

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 11-7 provides the questions included in each domain, the questions with the reversed scores, as well as the CFQ-R for Adolescents and Adults. The CFQ-R scoring manual is also attached.

Table 11-7 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.

The CFQ-R scoring manual is attached.

CFQR scoring manual.pdf

Appendix G: Imputation Rules for Missing AE dates

H.1 Parts 1 and 3

Imputation rules for missing or partial AE start date for Parts 1 and 3 are defined below.

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

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

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

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

- **If Year of AE start date is missing:**

  If the year of AE start is missing or AE start date is completely missing then query site with no imputation.
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then the AE will be considered as TEAE for the Treatment Period.
    - else the AE will be considered as a pretreatment AE.

H.2 Part 2

Imputation rules for missing or partial AE start date for Part 2 are defined below.

- **If only Day of AE start date is missing:**
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then

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

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

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

  Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE 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.

- If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then the AE will be considered as TEAE for the Treatment Period.
- else if the full (or partial) AE end date is NOT before the first dose date of the Run-in Period, then the AE will be considered as TEAE for the Run-in Period.
- else the AE will be considered as a pretreatment AE.

Imputation rules for partial AE end date are defined below:

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

Appendix H: Criteria for Threshold Analysis

Table 11-8 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Clinical Chemistry (LFT)		
ALT	>ULN - ≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >8x - ≤ 20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
AST	>ULN - ≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >8x - ≤ 20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
ALT or AST	(ALT>ULN - ≤ 3xULN) or (AST>ULN - ≤ 3xULN) (ALT>3x - ≤ 5xULN) or (AST>3x - ≤ 5xULN) (ALT>5x- ≤ 8xULN) or (AST>5x - ≤ 8xULN) (ALT>8x - ≤ 20xULN) or (AST>8x - ≤ 20xULN) ALT>20xULN or AST> 20 xULN	FDA DILI Guidance
Alkaline Phosphatase	>ULN - ≤ 1.5xULN >1.5 – ≤ 2.5 xULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>ULN - ≤ 1.5xULN >1.5 – ≤ 2xULN >2 – ≤ 3xULN >3 – ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
Direct Bilirubin	>ULN - ≤ 1.5xULN >1.5 – ≤ 2xULN >2 – ≤ 3xULN >3 – ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	FDA DILI Guidance Jul 2009.

Table 11-8 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
GGT	>ULN - ≤ 2.5xULN >2.5 – ≤ 5.0xULN >5.0 – ≤ 20.0xULN >20.0xULN	CTCAE grade 1-4
Clinical Chemistry (NON-LFT)		
Albumin	<LLN - ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>1x - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Creatinine	>ULN - ≤ 1.5xULN >1.5 - ≤ 3.0xULN >3.0 - ≤ 6.0xULN >6.0xULN	CTCAE grades 1-4
Lipase	>ULN - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
CPK	>ULN - ≤ 2.5 x ULN >2.5 - ≤ 5 x ULN >5 - ≤ 10x ULN >10 x ULN	CTCAE grades 1-4
Hematology		
Hemoglobin	Hgb decreased (anemia) <LLN - ≥ 100 g/L <100 – ≥ 80 g/L < 80 g/L	CTCAE grade 1-3
	Hgb increased >ULN - ≤ 20 g/L above ULN >20 g/L above ULN - ≤ 40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3
Platelets	Platelet decreased <LLN - ≥ 75.0 x 10e9 /L <75.0 – ≥ 50.0 x 10e9 /L <50.0 – ≥ 25.0 x 10e9 /L <25.0 x 10e9 /L	CTCAE grade 1-4
	Platelet increased >ULN	No CTCAE available

Table 11-8 Threshold Analysis Criteria for Laboratory Tests (as applicable)

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

Table 11-9 Threshold Analysis Criteria for ECGs

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

Table 11-9 Threshold Analysis Criteria for ECGs

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

Note: Based on CPMP 1997 guideline.

Table 11-10 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
Pulse Rate	Same as above in ECG category	
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	

Table 11-10 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
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 increased		
	>90 mmHg	
	>100 mmHg	
	>5 mmHg increase from baseline	
	>10 mmHg increase from baseline	
	>90 mmHg and >5 mmHg increase from baseline	
	>90 mmHg and >10 mmHg increase from baseline	
	>100 mmHg and >5 mmHg increase from baseline	
	>100 mmHg and >10 mmHg increase from baseline	
DBP decreased		
	<60 mmHg	
	<45 mmHg	
	>5 mmHg decrease from baseline	
	>10 mmHg decrease from baseline	
	<60 mmHg and >5 mmHg decrease from baseline	
	<60 mmHg and >10 mmHg decrease from baseline	
	<45 mmHg and >5 mmHg decrease from baseline	
	<45 mmHg and >10 mmHg decrease from baseline	

Table 11-10 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
Weight	Weight gain ≥5 % increase from baseline ≥10 % increase from baseline ≥ 20% increase from baseline	CTCAE grade 1-3
	Weight loss ≥5 % decrease from baseline ≥10 % decrease from baseline ≥ 20% decrease from baseline	CTCAE grade 1-3