1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan

Methods for Parts A, B and C

Protocol Number: VX16-445-001

A Phase 1/2 Study of VX-445 in Healthy Subjects and Subjects With Cystic Fibrosis

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3 INTRODUCTION

The statistical analysis plan (SAP) describes the statistical methods to be used for the interim analyses of safety data to support the preparation of regulatory submissions, and the final analysis and reporting of data collected under the approved clinical study protocol VX16-445-001 (Version 7.0 dated 08Aug2017), and approved case report forms (CRFs) (Version 1.0 dated 18Jan2017 for Part A (Cohort A1-A6, A8 and A9), Version 2.0 dated 03Apr2017 for Part A (Cohort A7), Version 3.0 dated 13Feb2017 for Part B, Version 1.0 dated 10Apr2017 for Part C).

This SAP addresses the safety objectives of the study and describes the planned safety statistical analyses and data presentations only for Parts A, B and C. All analyses and data presentations will be generated by Tigermed Clinical Research Limited, Biometrics group, using SAS® Version 9.4 software (SAS Institute, Cary, North Carolina, USA). This SAP will be finalized and approved before the data cut for the interim analyses. Any changes made to the SAP for the final analysis will be finalized and approved before the clinical database lock, and any changes made to the SAP after the clinical database lock will be documented and discussed in the clinical study report for this study.

4 STUDY OBJECTIVES

4.1 Primary Objectives

Part A

To evaluate the safety and tolerability of single ascending doses of VX-445 in healthy subjects

Part B

To evaluate the safety and tolerability of multiple ascending doses of VX-445 administered in healthy subjects

Part C

To evaluate the safety and tolerability of multiple doses of VX-445 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) for 14 days in healthy subjects

4.2 Secondary Objectives

Part A

- To evaluate the PK of VX-445 after administration of single ascending doses of VX-445 in healthy subjects
- To evaluate the effect of food on VX-445 PK in healthy subjects
- To evaluate the absolute bioavailability (BA) of VX-445 when administered orally relative to intravenous (IV) administration in healthy subjects

Part B

To evaluate the PK of VX-445 after multiple ascending doses of VX-445 administered to healthy subjects

Part C

- To evaluate the PK of VX-445 after multiple ascending doses of VX-445 in TC with TEZ and IVA for 14 days in healthy subjects
- To evaluate the PK of TEZ and metabolites (M1-TEZ and M2-TEZ), and IVA and metabolites (M1-IVA and M6-IVA) after administration in TC with VX-445 for 14 days in healthy subjects

5 STUDY ENDPOINTS

5.1 Primary Endpoints

Safety and tolerability based on the assessment of adverse events (AEs), clinically significant laboratory test results, standard 12-lead electrocardiograms (ECGs), vital signs, and spirometry (Parts B and C only).

5.2 Secondary Endpoints

Parts A and B:

PK parameter estimates of VX-445 derived from plasma concentration-time data

Part C:

- PK parameter estimates of VX-445 derived from plasma concentration-time data
- PK parameter estimates for TEZ and metabolites (M1-TEZ and M2-TEZ), and IVA and metabolites (M1-IVA and M6-IVA) derived from plasma concentration-time data

[redacted]

6 STUDY DESIGN

6.1 Overall Design

This is a first-in-human study of VX-445. Approximately 120 healthy subjects will be enrolled for Parts A, B, and C.

No subject will be allowed to randomize to more than 1 dose cohort.

Parts A, B, and C are randomized, double-blind, placebo-controlled, single- and multiple-dose parts in healthy subjects of this first-in-human study of VX-445. Part A also includes an evaluation of the effect of food on VX-445 PK and an evaluation of absolute BA. Part C doses VX-445 in TC with TEZ/IVA.

There is no pre-specified ratio of males to females, but reasonable effort will be made to enroll females of non-childbearing potential in all dosing cohorts.

A schematic of the study design for Parts A, B, and C is shown in Table 6-1.

Number of Cohorts

In Parts A and B, 6 dose escalation cohorts are planned, although fewer than 6 or up to 2 additional cohorts may be enrolled in each part, based on data from previous cohorts. The additional cohorts will follow the corresponding schedule of assessments. In Part C, 2 cohorts are

planned, while fewer or up to 2 additional cohorts each may be enrolled based on data from previous cohorts. The decision to initiate successive cohorts and dose selection will be based on safety, tolerability, and available PK data from preceding cohort(s). Refer to Section 9.7.1 of the protocol for dose escalation criteria and Section 9.8.1 of the protocol for stopping criteria.

Staggering of Dosing

In Cohort A1 (first single dose cohort) and in Cohort C1 (first TC cohort), dosing will be staggered so that 2 subjects are dosed (Cohort A1: 1 with VX-445 and 1 with placebo; Cohort C1: 1 with TC and 1 with triple placebo) at least 24 hours before the remaining 6 subjects in each cohort. Doses may be staggered in other cohorts if deemed necessary based on review of emerging safety data.

Timing of Part B and C Initiation

Part B may be initiated while Part A is ongoing after review of safety, tolerability, and PK data.

Part C may be initiated while Parts A and B are ongoing after review of safety, tolerability, and PK data.

Starting Dose in Parts B and C

Information about the starting doses of Cohorts B1 and C1 can be found in Table 6-1 and Section 9.3.2.1 of the protocol.

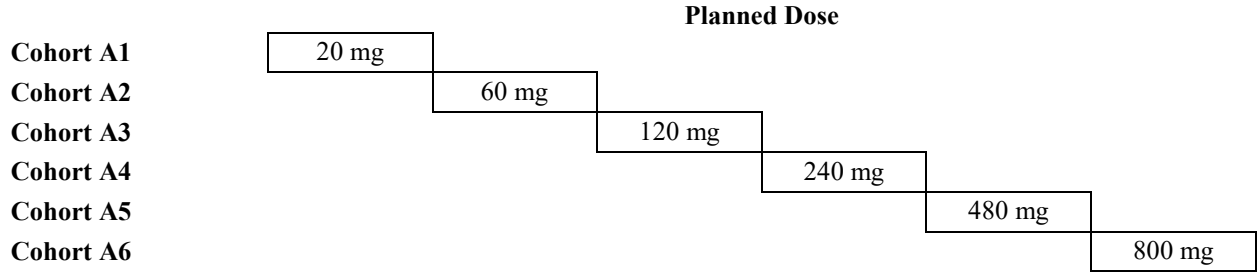
Table 6-1 Study Design for Parts A, B, and C

Part A: Single-dose escalation of VX-445

Cohorts A1 to A6: 8 subjects per cohort, randomized 3:1 (VX-445:placebo). Planned doses are shown; doses may be modified upward or downward based on emerging data.

Cohort A7: 8 subjects. VX-445 tablet dose is TBD, pending PK data from previous Part A cohorts, but will not exceed the highest dose that was safe and well tolerated. The planned IV dose is 20 mg.

No dose increment will be predicted to yield greater than a 3-fold increase (Cohorts A1 through A3) or a 2-fold increase (all other Part A cohorts except Cohort A7) in exposure from the preceding dose level.



Cohort A7 (open label VX-445, single sequence)[a]

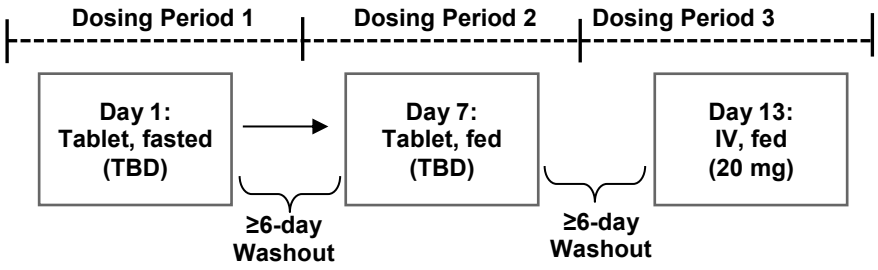
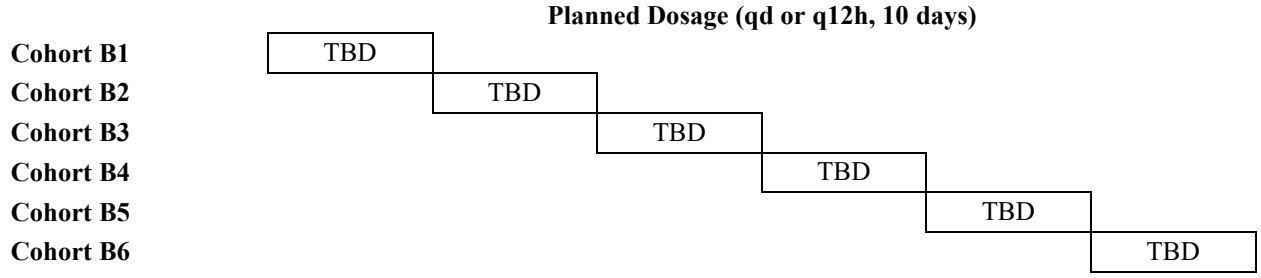


Table 6-1 Study Design for Parts A, B, and C

Part B: Multiple-dose escalation of VX-445

8 subjects per cohort, randomized 3:1 (VX-445:placebo)

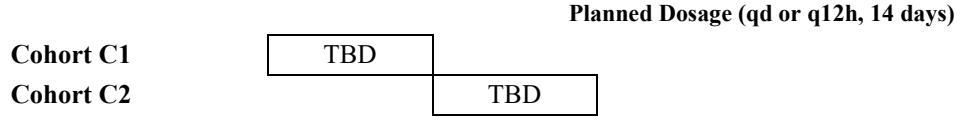
The total daily dose in Cohort B1 will be at least 1 dose level below the highest Part A dose for which safety, tolerability, and PK results are available and that is safe and well tolerated.



Part C: Multiple-dose escalation of VX-445 in TC with TEZ/IVA[b]

8 subjects per cohort, randomized 3:1 (VX-445/TEZ/IVA:triple placebo)

The starting dose for Part C (Cohort C1) will be at least 1 dose level below the highest Part B dose for which safety and tolerability results are available and supportive.



CRU: clinical research unit; IV: intravenous; IVA: ivacaftor; PK: pharmacokinetic; q12h: every 12 hours; qd: once daily; TBD: to be determined; TC: triple combination (VX-445/TEZ/IVA); TEZ: tezacaftor

Note: Dose escalation criteria are described in Section 9.7.1 of the protocol, and dose escalation will be stopped when the predefined stopping criteria is met (see Section 9.8.1of the protocol).

[a] The Washout Period is a minimum of 6 days and may be increased as needed based on emerging data from earlier cohorts (Cohorts A1 through A6). Subjects in Cohort A7 will receive a single dose of VX-445 on up to 3 dosing occasions. VX-445 doses include 2 single oral doses of tablet (dose TBD, pending PK data from previous Part A cohorts, but will not exceed the highest dose that was safe and well tolerated) and a single IV dose (the planned dose is 20 mg, but may be adjusted pending data from previous Part A cohorts; however, the final selected dose will not be predicted to exceed the highest exposure that was safe and well tolerated). If the IV formulation or the data supporting the use of the IV formulation are not available, then the third dosing period, in which subjects receive the IV dose, will not be conducted. If the IV dose is not administered, subjects will be discharged from the CRU on Day 13 after completing all study visit assessments and will return for a Safety Follow-up Visit (Table 12-3).

[b] The dosage of TEZ/IVA will be TEZ 100 mg qd/IVA 150 mg q12h which will be administered as TEZ 100-mg/IVA 150-mg FDC in the morning and IVA 150 mg in the evening.

6.2 Sample Size and Power

No formal sample size calculations have been performed. The number of subjects participating in each cohort is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study.

6.3 Randomization

A randomization list for each part will be produced by Vertex Biostatistics or a qualified randomization vendor. The Vertex study biostatistician will review and approve the dummy randomization list. The final randomization list will be reviewed and approved by a designated unblinded biostatistician who is not a member of the study execution team (SET).

Only subjects who have completed screening assessments and are eligible for participation in the study will be randomized to receive active study drug or placebo. Randomized subjects will be assigned a unique subject number. A list identifying subjects by their subject number will be maintained in the study file at the CRU.

6.4 Replacement

Subjects who withdraw or are withdrawn before the first dose of study drug on Day 1 for each part may be replaced.

Subjects who withdraw or are withdrawn for non-safety reasons during the study drug treatment periods may be replaced at Vertex's discretion.

6.5 Blinding and Unblinding

This will be a double-blind study with the exception of Cohort A7, which will be open-label.

6.5.1 Blinding

Blinding of subject treatment assignments will be maintained until database lock. The packaging and labeling of study drug will be done to ensure that treatment assignments are blinded within each cohort in all parts of the study.

During the conduct of the study, all study personnel will be blinded to subject treatment assignments except for

- the unblinded site monitor;
- Bioanalytical CRO analyzing PK samples and Vertex Bioanalytical personnel who is not a member of the SET but reviews raw data from Bioanalytical CRO. The Vertex Bioanalytical SET member will continue to be blinded;
- vendor preparing the unblinded statistical and PK/PD analysis of continuous ECG data collected in Part A(with the exception of Cohort A7);
- the unblinded biostatistician preparing the randomization list as well as an unblinded quality control (QC) biostatistician;
- the dispensing contracted pharmacist;
- the pharmacy QC/quality assurance personnel, as applicable; and
- Vertex GPS and Regulatory Affairs, when required to satisfy regulatory reporting requirements.

The Vertex medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time.

A limited Vertex team, which may include members of the Vertex SET, may be unblinded to individual subject treatment assignments for the purposes of review of PD, PK/PD, and/or safety data. No unblinded data or results of unblinded analyses will be shared with the clinical research unit or with blinded Vertex personnel. All instances of unblinding by Vertex personnel will be documented.

Bioanalytical results (i.e., concentrations of VX-445) will be reported by the bioanalytical CRO using masked identification numbers for PK analysis.

6.5.2 Unblinding

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

Unblinding of 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. In case of emergency, the investigator will have the final decision and unilateral right for unblinding.

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

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

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor 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 a serious adverse event (SAE), according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to 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 also 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.

Unblinding: Interim Analysis Results

When an IA is performed after all subjects in Part C have completed the Safety Follow-up Visit, results from Parts A, B, and C will be unblinded for full review by the Vertex study team.

[redacted]

8 ANALYSIS SETS

8.1 All Subjects Set

The All Subjects Set is defined as all subjects who were randomized or received at least 1 dose of study drug. The All Subjects Set will be used for individual subject data listings, and the disposition summary table, unless specified otherwise.

8.2 Safety Set

The Safety Set will include all subjects who received at least 1 dose of study drug. All safety, demographics, baseline characteristics, study drug exposure, and concomitant medications will be summarized for the Safety Set.

[redacted]

9 STATISTICAL ANALYSIS

9.1 General Considerations

The Schedule of Assessments is provided in Appendix A.

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

Continuous data will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), standard error (SE), median, minimum value (min), and maximum value (max). Unless otherwise specified, minimum and maximum

values will be reported with the same precision as the units of the raw data. The mean, median, SD, and SE will be reported to 1 additional decimal place. Any values that require a transformation to standard units (metric or International System [SI]) will be converted with the appropriate precision.

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

Treatment Emergent (TE) Periods:

For subjects included in all cohorts in Parts A (except Cohort A7), B and C, One single TE period will begin from the initial administration of study drug through the Safety Follow-up Visit.

Treatment Groups

The Treatment Groups in Part A (excluding Cohort A7), Parts B and C will be defined as the corresponding dose groups.

For subjects participating in Cohort A7 in Part A, 3 TE periods will be analyzed:

- **TE Period 1 (tablet [fasted])** will begin from the initial administration of study drug on Day 1 until the administration of study drug on Day 7.
- **TE Period 2 (tablet [fed])** will begin from the initial administration of study drug on Day 7 until the administration of study drug on Day 13.
- **TE Period 3 (IV [fed])** will begin from the initial administration of study drug on Day 13 through the Safety Follow-up Visit.
- The 3 **Treatment Groups** in Cohort A7 will correspond to tablet [fasted], tablet [fed] and IV [fed] respectively.

Baseline value:

The baseline value will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first administration of study drug on Day 1. If a pre-dose measurement is missing and no drug-free unscheduled assessments are performed before the first dose of the study, the baseline will be missing. 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.

For Cohort A7

The baseline value will be defined as the most recent non-missing measurement collected before the initial administration of study drug on Day 1. If the pre-dose measurement is missing and no drug-free unscheduled assessments are performed before the first dose of study drug, the baseline value will be determined to be missing.

Change from baseline value will be defined as change from baseline at each scheduled post-baseline time point. The change from baseline value will be calculated as the post-baseline value minus the baseline value.

Visit Window: As the majority of assessments are predicted to be on schedule, visit windows will not add significant value to the analysis and will not be applied.

Unscheduled visits: Subject data obtained during unscheduled visits will not be summarized but will be included in subject data listings only, except for the ECG analysis of the maximum values during TE period and maximum changes from baseline in QT/QTcF intervals during TE period (see Protocol Section 11.7.5). Unscheduled visit values will not be used to impute missing scheduled visit values, except for baseline calculation.

Incomplete/missing data (e.g., dates, post-baseline values) will not be imputed, unless otherwise specified; i.e., all missing values and missing post-baseline values will remain as missing in all statistical analyses and listings, unless otherwise specified.

Outliers: No formal statistical analyses will be performed to detect and/or remedy the presence of statistical outliers.

Hypothesis testing: No statistical hypothesis testing will be performed.

All subject level data, including those derived, will be presented in the individual subject data listings; listings will be based on the All Subjects Set.

Unless otherwise specified, the analyses will be done by Treatment Group in all cohorts for Parts A, B and C. Separate summary tables will be produced for each part.

- Part A (Cohorts A1 through A5): Placebo, VX-445 20 mg, VX-445 60 mg, VX-445 120 mg, VX-445 240 mg, VX-445 360 mg, and VX-445 Total. The dose levels are subject to change to reflect the real dose levels.

- Part A (Cohort A7): tablet [fasted] 100 mg, tablet [fed] 100 mg and IV [fed] 20 mg.

- Part B: Placebo, VX-445 60 mg QD, VX-445 120 mg QD, VX-445 240 mg QD, VX-445 340 mg QD and VX-445 Total.

- Part C: Triple Placebo, VX-445 200 mg QD + TEZ/IVA, VX-445 280 mg QD + TEZ/IVA, VX-445 100 mg QD + TEZ/IVA and VX-445 + TEZ/IVA Total.

9.2 Background Characteristics

9.2.1 Subject Disposition

Disposition summary will be based on the All Subjects Set.

The number and percentage of subjects in each disposition category (randomized; included in the Safety Set; PD set; completed dosing; completed study; discontinued treatment for Cohort A7 and for all cohorts in Parts B and C, and discontinued study with a breakdown of the reasons for early discontinuation, when applicable) will be summarized overall and by Treatment Group for Parts A (Cohorts A1 through A6), B and C, and by treatment sequence for Cohort A7.

9.2.2 Demographics and Baseline Characteristics

Demographics, medical history and baseline characteristics summary will be based on the Safety Set.

Demographics and baseline characteristics (age, sex, race, ethnicity, weight, height, BMI, medical history, baseline spirometry [Parts B and C] [redacted] will

be summarized overall and by Treatment Group for Parts A (Cohorts A1 through A6),B and C, and by sequence for Cohort A7.

No statistical tests will be done to evaluate baseline imbalances between groups.

9.2.3 Prior and Concomitant Medications

Medications will be coded using the World Health Organization-Drug Dictionary Enhanced (WHO-DDE) 1st March 2016, Format B2 or higher. Medications used in the study will be categorized as prior and/or concomitant medications as follows:

1. **Prior medication**: Medication that started before the first dose of study drug, regardless of when dosing of the medication ended
2. **Concomitant medication**: Medication received at or after the first dose of study drug, medication that was received before initial dosing and continued after initial dosing of study drug, or medication with missing stop date

If a medication start date is on or after the date of initial dosing of the study drug, then the medication will be summarized as concomitant medication regardless of whether the medication end date is missing or not. If a medication end date is before the date of initial dosing of the study drug, then the medication will be summarized as prior medication regardless of whether the medication start date is missing or not. Note that medication that started before initial dosing of the study drug and continued after initial dosing will be summarized as prior medication and separately as concomitant medication.

Missing or partial dates will be imputed for medication. Algorithm for missing or partial start date is:

Missing day: first day of the month is imputed;
Missing month: January is imputed;
Missing year: not imputed.

Algorithm for missing or partial end date is:

Missing day: last day of the month is imputed;
Missing month: December is imputed (31 December if day is also missing);
Missing year: not imputed.

Missing data algorithms will be reviewed to ensure the algorithm works. For example, end date will not be before the start date after the imputation.

For Cohort A7, concomitant medications will be assigned to each TE period based on the start date of the medication and the study drug administration dates (concomitant medications taken during the TE period will be assigned to the TE period, and so forth).

Note that a concomitant medication may be assigned to multiple TE periods.

Prior medications will not be summarized, but will only be listed. Concomitant medications will be summarized using preferred name by Treatment Group and overall for all cohorts in Parts A (except for Cohort A7), B and C, and by Treatment Group only for Cohort A7. Concomitant Medications summary will be based on the Safety Set.

9.2.4 Study Drug Exposure and Compliance

Study drug exposure (i.e., duration of treatment) will be summarized by Treatment Group and overall for all cohorts in Parts B and C for the Safety Set.

Study drug exposure (in days) will be defined as (last date of dosing – first date of dosing) + 1.

The study drug administration will be presented in an individual subject listing for Parts A, B and C.

9.3 Safety Analysis

Safety is the primary objective of this study. The overall safety profile of VX-445 will be assessed in terms of the following primary (safety) endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (including coagulation studies)
- ECG outcomes
- Vital signs
- Spirometry (Parts B and C only)

Safety analyses will be performed by Treatment Group and overall for all cohorts in Parts A (except for cohort A7), B and C, and by Treatment Group only for Cohort A7. Safety analysis will be conducted for the Safety Set. Safety data will be presented in the individual subject data listings based on the All Subjects Set. Only descriptive analysis of safety will be performed (i.e., no statistical hypothesis testing will be performed).

Table 9-1 shows the safety summaries (e.g., raw value, change from baseline, incidence, and clinical abnormalities) that will be summarized for TEAEs, clinical laboratory values, 12-lead ECG, vital signs, spirometry (Parts B and C), and physical examination. Details are provided in the corresponding subsections.

The incidence of TEAEs will be summarized. TEAE summaries will include the following: all TEAEs (regardless of severity or relationship to study drug), serious adverse events (SAEs), TEAE severity, TEAE relationship, and discontinuations of study drug treatment due to TEAEs.

For the non-AE safety evaluations (clinical laboratory, spirometry, ECGs and vital signs), raw values, and changes from baseline will be summarized as indicated in Table 9-1. For example, an "X" under the raw value column (second column) means that the raw values for the safety evaluation will be summarized; an "X" under the Change column (third column) means that change will be summarized.

Throughout this section, "change" refers to absolute change from baseline.

Table 9-1 Summaries Planned for Safety Data

Safety Assessment	Incidence	Raw Value	Change	Clinical Abnormalities
TEAEs	X			Not applicable
Hematology and chemistry		X	X	Present in listing only
Coagulation		Present in listing only		Present in listing only
Urinalysis		Present in listing only		Present in listing only
12-lead ECG		X	X	Present in listing only
Vital signs		X	X	Not applicable
Spirometry (Parts B and C)		X	X	Not applicable
Physical Examination		Present in listing only		Not applicable

ECG: electrocardiogram; TEAEs: treatment-emergent adverse events; X: safety assessment will be summarized in tables.

9.3.1 Adverse Events

AEs will be coded according to MedDRA (Version 19.1 or above). The number and percentage of subjects experiencing an AE will be summarized by the MedDRA System Organ Class (SOC) and Preferred Term (PT). AEs will be classified as pretreatment or treatment-emergent.

Pretreatment AEs are defined as AEs that were reported or worsened after signing the ICF up to the start of study drug dosing.

Treatment-emergent adverse events (TEAEs) for all cohorts except Cohort A7 are defined as AEs that started or worsened on or after the start of study drug dosing within the TE Period.

For Cohort A7, TEAEs will be assigned to each Treatment Group based on the start date of the AE and the start of study drug administration dates within the corresponding TE Period.

AE summary tables will be presented for TEAEs only and will include the following: (1) all TEAEs; (2) related (defined as possibly related, related, or unknown) TEAEs; (3) serious TEAEs; (4) TEAEs by severity; (5) TEAEs by relationship; and (6) TEAEs leading to treatment discontinuation. Summaries will be presented by MedDRA SOC and PT using frequency counts and percentages by Treatment Group and overall for each part. A subject with multiple occurrences of the same TEAE or a continuing TEAE will be counted only once under the highest reported severity and relationship. In addition, a listing containing individual subject AEs leading to death, SAEs, dose interruption, and permanent discontinuation will be listed separately. All AEs will be presented in individual subject data listings.

9.3.2 Clinical Laboratory

All statistical analyses of laboratory values will be performed using SI units. Continuous hematology and chemistry results including baseline and change from baseline values will be summarized at each scheduled time point by Treatment Group and overall for Parts A (except Cohort A7), B and C, and by Treatment Group only for Cohort A7 using descriptive statistics.

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

Urinalysis results will only be listed in individual subject data listings and will not be summarized.

Clinically significant abnormal findings will be reported as AEs.

9.3.3 Electrocardiogram

A summary of raw values and change from baseline values will be provided for each scheduled time point by Treatment Group and overall for Parts A (except Cohort A7), B and C, and by Treatment Group only for Cohort A7 during the TE Period for the following 12-lead ECG measurements using descriptive statistics: PR, RR, QT, QRS, and QTc intervals and heart rate.

In addition, the number and percentage of subjects by maximum value of QT/QTc intervals during the TE period, categorized as ≤450 msec, >450 msec and ≤480 msec, >480 msec and ≤500 msec, and >500 msec, as well as maximum change from baseline value of QT/QTc intervals during the TE period, categorized as ≤0 msec, >0 msec and ≤30 msec, >30 msec and ≤60 msec, and >60 msec will be tabulated based on scheduled and unscheduled 12-lead ECG measurements.

Clinically significant abnormal findings will be reported as AEs.

9.3.4 Vital Signs

A summary of raw values and change from baseline values will be provided for each scheduled time point by Treatment Group and overall for Parts A (Cohorts A1 through A6), B and C, and by Treatment Group only for Cohort A7 using descriptive statistics for the following vital signs measurements: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute).

Clinically significant abnormal findings in vital signs will be reported as AEs.

9.3.5 Physical Examination

PE results will be presented in individual subject data listings only. Clinically relevant changes identified after screening will be reported as AEs.

9.3.6 Spirometry (Parts B and C Only)

The spirometry assessment will be administered in Part B and C only. A summary of raw values and change from baseline values will be provided for each scheduled time point by Treatment Group and overall for all cohorts in Parts B and C. The following spirometry parameters of FEV_1 (L) and $ppFEV_1$, FVC (L) and ppFVC, FEV_1/FVC (ratio) and $ppFEV_1$/FVC as well as $FEF_{25\%-75\%}$ (L/s) and $ppFEF_{25\%-75\%}$ will be summarized using descriptive statistics.

In addition, a listing containing individual subject data with scheduled and unscheduled time points will be provided.

9.3.7 Other Safety Analyses

Not applicable.

[redacted]

[redacted]

9.5 Other Analysis

Not applicable.

10 SUMMARY OF INTERIM AND IDMC ANALYSES

Separate **interim analyses of safety data** may be performed after

- all subjects in Cohort C1 have completed the Safety Follow-up Visit;
- all subjects in Cohort C2 have completed the Safety Follow-up Visit;

The interim analyses might be blinded or unblinded depending on the decision of VX-445 Study Team. If an unblinded interim analysis is decided, the unblinded results will be reviewed by a limited unblinded Vertex group not involved in the conduct of the study.

Continuous ECG

An interim analysis of the continuous ECG data may be performed after all subjects in Part A (with the exception of Cohort A7) have completed the Safety Follow-up Visit. These results will be reviewed by a small unblinded Vertex team not involved in the conduct of the study.

The analysis of the continuous ECG data will be performed [redacted] The analysis plan was documented in the SAP for the continuous ECG, version 1.0, dated 17 May 2017.

An **interim analysis** for Parts A, B, and C may be performed after all subjects in Part C have completed the Safety Follow-up Visit. The results of this analysis will be unblinded for full review by the Vertex study team.

10.1 Summary of Flow of Data for Interim Analysis of Safety Data

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

1. The unblinded Biometrics group [redacted], will download the treatment codes directly [redacted];

2. [redacted] will generate the unblinded outputs (tables, figures and listings) and upload [redacted] for retrieval by the limited unblinded Vertex team.

10.2 Summary of Flow of Data for Continuous ECG Interim Analysis

To protect the scientific integrity of the treatment assignments, the following steps for the flow of continuous ECG data will be executed for the interim analysis:

1. [redacted] will access the password-protected production randomization data from a Vertex Biometrics [redacted];
2. [redacted] with the password to open the production randomization data file;
3. [redacted] will generate the unblinded outputs (tables and figures) for review by a limited unblinded Vertex group.

10.3 IDMC Analysis

Not applicable.

11 REFERENCES

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. EurRespir J. 2012; 40 (6):1324-43.

12 APPENDICES

Appendix A Schedule of Assessments

Schedules of Assessments are shown in Table 12-1 (Screening, Parts A through C), Table 12-2 (Part A, Cohorts A1 through A6), Table 12-3 (Part A, Cohort A7), Table 12-4 (Part B), and Table 12-5 (Part C).

Table 12-1 Study VX16-445-001: Parts A, B, and C, Screening

Event/Assessment	Screening Visit Day -28 to Day -2
Informed consent	X
Demographics	X
Medical history	X
Medications review[a]	X
Height, weight, BMI, and vital signs[b]	X
Full PE	X
Standard 12-lead ECG[c]	X
Serum FSH (suspected postmenopausal female subjects only)	X
Serum β-hCG (all female subjects)	X
Serology (HBsAg, HCV, HIV-1 and HIV-2 Abs, and p24 antigen)	X
G6PD activity test[d]	X
Serum chemistry[e]	X
Hematology[e]	X
Coagulation[e]	X
Drug test (urine or blood), including cotinine	X
Alcohol test (urine, blood, or breath)	X
Urinalysis	X
Spirometry (Parts B and C only)	X
[redacted]	
AEs	Continuous from signing of ICF through Safety Follow-up Visit

AE: adverse event; β-hCG: beta-human chorionic gonadotropin; BMI: body mass index; ECG: electrocardiogram; FSH: follicle-stimulating hormone; G6PD: glucose-6-phosphate dehydrogenase; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV-1/HIV-2 Abs: antibodies against human immunodeficiency viruses 1 and 2; ICF: informed consent form; PE: physical examination

[a] All medications taken within 28 days before the first dose of study drug through the end of the study will be recorded.
[b] Weight and height will be measured with shoes off. Vital signs will be performed after the subject has been seated for at least 5 minutes.
[c] A standard 12-lead ECG will be performed after the subject has been seated or supine for at least 5 minutes (Section 11.7.5.1 of the protocol).
[d] A single blood sample will be collected from all subjects for the G6PD activity test.
[e] Following at least a 4-hour fast, blood samples will be collected for clinical laboratory assessments.
[redacted]

Table 12-2 Study VX16-445-001: Part A, Cohorts A1 Through A6, Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Study Day						Safety Follow-up Visit (7 to 10 days After Last Dose of Study Drug)
	-1	1	2	3	4	5	
Inpatient days	X	X	X	X	X	X[b]	
Outpatient visit							X
Randomization		X					
Weight[c]	X						
Continuous ECGs[d]		X	X				
Standard 12-lead ECG[e]	X	X					X
Vital signs[f]	X	X	X	X	X	X	X
Full PE	X						X
Serum chemistry	X		X				X
Hematology	X		X				X
Blood for PK analysis[g]		X	X	X	X	X	
Drug test (urine or blood), including cotinine	X						
Alcohol test (urine, blood, or breath)	X						
Urinalysis							X
Study drug administration[h]		X					
AEs	Continuous from signing of ICF through Safety Follow-up Visit						
Medications review[i]	Continuous from signing of ICF through Safety Follow-up Visit						

AE: adverse event; CRU: clinical research unit; ECG: electrocardiogram; ICF: informed consent form; PE: physical examination; PK: pharmacokinetic

[a] On dosing days, assessments will be performed before dosing, unless noted otherwise.
[b] Subjects will be discharged from the CRU on Day 5 after completion of the study visit assessments.
[c] Weight will be measured with shoes off.
[d] Continuous ECGs will be extracted in up to 10 replicates on Day 1 before dosing (at -60, -50, and -40 minutes) and at 1, 2, 3, 4, 6, 8, 12 and 24 hours (Day 2) after dosing. Subjects should be supine or semi-recumbent for at least 15 minutes before these time points.
[e] Standard 12-lead ECGs will be performed after the subject has been seated or supine for at least 5 minutes. On Day 1, ECGs will be collected before dosing and approximately 1, 3, 5, and 6 hours (± 15 min) after dosing.
[f] Vital signs will be performed after the subject has been seated for at least 5 minutes.
[g] Blood samples for PK assessments will be collected on Day 1 before dosing (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 (Day 2), 36 (Day 2), 48 (Day 3), 72 (Day 4), and 96 (Day 5) hours after dosing. Acceptable PK sampling windows are provided in Table 11-1 of the protocol.
[h] Study drug will be administered in the fed state. Details are provided in Section 9.6.1.1 of the protocol.
[i] All medications taken from 28 days before the first dose of study drug through the end of the study will be recorded.

Table 12-3 Study VX16-445-001: Part A, Cohort A7, Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Study Day																		Safety Follow-up Visit (7 to 10 Days After Last Dose of Study Drug)
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14[b]	15[b]	16[b]	17[b]	
Inpatient days	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]	X	X	X	X[d]	
Outpatient visit																			X
Weight[e]	X																		
Standard 12-lead ECG[f]	X	X						X						X					X
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full PE	X																		X
Serum chemistry	X		X						X						X				X
Hematology	X		X						X						X				X

[a] On dosing days, assessments will be performed before dosing, unless noted otherwise.
[b] If data to support use of the IV dose is not available, Dosing Period 3 will not be conducted and assessments on Days 14 to 17 will not be performed.
[c] Subjects will be discharged from the CRU on Day 13 after completion of the study visit assessments if Dosing Period 3 is not conducted.
[d] Subjects will be discharged from the CRU on Day 17 after completion of the study visit assessments.
[e] Weight will be measured with shoes off.
[f] Standard 12-lead ECGs will be performed after the subject has been seated or supine for at least 5 minutes. On Days 1, 7 and 13, ECGs will be collected before dosing and approximately 1, 3, 5, and 6 hours (± 15 min) after dosing.
[g] Vital signs will be performed after the subject has been seated for at least 5 minutes.

Table 12-3 Study VX16-445-001: Part A, Cohort A7, Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Study Day																		Safety Follow-up Visit (7 to 10 Days After Last Dose of Study Drug)
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14[b]	15[b]	16[b]	17[b]	
Blood for PK analysis[h]		X	X	X	X	X	X	X	X	X	X	X	X	X[i]	X	X	X	X	
Drug test (urine or blood), including cotinine	X																		
Alcohol test (urine, blood, or breath)	X																		
Urinalysis																			X
Study drug adminstration[j]		X						X						X[k]					
AEs	Continuous from signing of ICF through Safety Follow-up Visit																		
Medications review[l]	Continuous from signing of ICF through Safety Follow-up Visit																		

AE: adverse event; CRU: clinical research unit; ECG: electrocardiogram; ICF: informed consent form; IV: intravenous; PE: physical examination; PK: pharmacokinetic

[h] Blood samples for PK assessments will be collected on Days 1 and 7 before dosing (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 (Days 2, 8), 36 (Days 2, 8), 48 (Days 3, 9), 72 (Days 4, 10), 96 (Days 5 and 11), and 120 (Days 6 and 12) hours postdose. Blood samples for PK assessments will be collected on Day 13 before dosing (0 hours, before the start of the IV infusion) and at 0.5 (after the end of the IV infusion), 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 (Day 14), 36 (Day 14), 48 (Day 15), 72 (Day 16), and 96 hours (Day 17) after the start of the IV infusion. Acceptable PK sampling windows are provided in Table 11-1 of the protocol.

[i] If Dosing Period 3 is not conducted, a blood sample for PK assessment will be collected on Day 13 (144 hours after dosing on Day 7).

[j] Study drug will be administered as a tablet in the fasted state on Day 1 and in the fed state on Day 7. On Day 13, study drug will be administered in the fed state as a single IV dose infused over 30 minutes (See Section 9.6.1.1 of the protocol for details). If the IV dose is not administered, subjects will be discharged on Day 13 after completion of the study visit assessments.

[k] If data to support use of the IV dose is not available, Dosing Period 3 will not be conducted and subjects will not receive the IV dose.

[l] All medications taken from 28 days before the first dose of study drug through the end of the study will be recorded.

Table 12-4 Study VX16-445-001: Part B, Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Study Day															Safety Follow-up Visit (7 to 10 Days After Last Dose of Study Drug)
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Inpatient days	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	
Outpatient visits																X
Randomization		X														
Weight[c]	X										X					
Standard 12-lead ECG[d]	X	X				X										X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full PE	X															X
Serum chemistry	X		X		X		X				X					X
Hematology	X		X		X		X				X					X
4β-hydroxycholesterol		X									X					
Blood for PK analysis[f]		X	X	X	X						X	X	X	X	X	
Drug test (urine or blood), including cotinine	X															
Alcohol test (urine, blood, or breath)	X															
Urinalysis																X

[a] On dosing days, assessments will be performed before dosing, unless noted otherwise. If Part B study drug is administered every q12h, assessments on dosing days will be performed relative to the morning dose only.

[b] Subjects will be discharged from the CRU on Day 14 after completion of the study visit assessments.

[c] Weight will be measured with shoes off.

[d] Standard 12-lead ECGs will be performed after the subject has been seated or supine for at least 5 minutes. On Days 1 and 5, ECGs will be collected before dosing and at approximately 1, 3, 5, and 6 hours (± 15 min) after dosing.

[e] Vital signs will be performed after the subject has been seated for at least 5 minutes.

[f] Blood samples for PK assessments of VX-445 will be collected on Day 1 before dosing (0 hours), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours after dosing. If dosing is q12h, the 12-hour sample will be collected before the next administered dose. On Days 2, 3, and 4, a blood sample will be collected in the morning before dosing. On Day 10, blood samples for PK assessments will be collected before dosing (0 hours), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 (Day 11), 36 (Day 11), 48 (Day 12), 72 (Day 13), and 96 (Day 14) hours after dosing. The acceptable PK sampling windows are provided in Table 11-1 of the protocol.

Table 12-4 Study VX16-445-001: Part B, Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Study Day															Safety Follow-up Visit (7 to 10 Days After Last Dose of Study Drug)
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Spirometry[g]	X	X								X						
Study drug administration[h]		X	X	X	X	X	X	X	X	X	X					
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit															
Medications review[i]	Continuous from signing of ICF through Safety Follow-up Visit															

CRU: clinical research unit; ECG: electrocardiogram; ICF: informed consent form; PK: pharmacokinetic; q12h: every 12 hours

[g] On Day 1, spirometry will be performed approximately 6 hours (± 1 hour) after dosing. On Day 9, spirometry will be performed before dosing and at approximately 6 hours (± 1 hour) after dosing. The assessment on Day -1 will be performed at approximately the same time of day (± 2 hours) as the nominal time of the 6-hour postdose assessments on Days 1 and 9.

[h] Study drug will be administered in the fed state (see Section 9.6.1.2 of the protocol) If dosing is q12h, the last dose of study drug will be administered on the morning of Day 10.

[i] All medications taken from 28 days before the first dose of study drug through the end of the study will be recorded.

Table 12-5 Study VX16-445-001: Part C, Treatment Period and Safety Follow-up Visit

	Study Day																			Safety Follow-up (7 to 10 Days After Last Dose of Study Drug)
Event/Assessment[a]	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Inpatient days	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	
Outpatient visits																				X
Randomization		X																		
Weight	X														X					
Standard 12-lead ECG[c]	X	X						X												X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full PE	X																			X
Serum chemistry	X		X			X				X					X					X
Hematology	X		X			X				X					X					X
[redacted]																				
Blood for VX-445 PK analysis[e]		X	X	X	X	X		X	X						X	X	X	X	X	
Blood for TEZ/IVA PK analysis[f]		X	X	X	X	X		X	X						X	X	X	X	X	

[a] On dosing days, assessments will be performed before dosing, unless noted otherwise, and will be performed relative to the morning dose only.

[b] Subjects will be discharged from the CRU on Day 18 after completion of the study visit assessments.

[c] Standard 12-lead ECGs will be performed after the subject has been seated or supine for at least 5 minutes. On Days 1 and 7, ECGs will be collected before dosing and approximately 1, 3, 5, and 6 hours (± 15 min) after dosing.

[d] Vital signs will be performed after the subject has been seated for at least 5 minutes.

[e] Blood samples for PK assessments of VX-445 will be collected on Day 1 and Day 7 before dosing (0 hours) and at 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours after dosing. The 12-hour sample will be collected before the next administered dose if dosing is q12h. On Days 2, 3, 4, 5, and 8, blood samples will be collected before (morning) dosing. On Day 14, blood samples will be collected before dosing (0 hours), and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24 (Day 15), 36 (Day 15), 48 (Day 16), 72 (Day 17), and 96 (Day 18) hours after dosing. Acceptable PK sampling windows are provided in Table 11-1 of the protocol.

[f] Blood samples for PK assessments of TEZ and metabolites, and IVA and metabolites will be collected on Day 1 and Day 7 before dosing (0 hours) and at 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours after dosing. The 12-hour sample will be collected before the next administered IVA dose. On Days 2, 3, 4, 5, and 8, blood samples will be collected before (morning) dosing. On Day 14, blood samples will be collected before dosing (0 hours), and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24 (Day 15), 36 (Day 15), 48 (Day 16), 72 (Day 17), and 96 (Day 18) hours after dosing. Acceptable PK sampling windows are provided in Table 11-1 of the protocol.

Table 12-5 Study VX16-445-001: Part C, Treatment Period and Safety Follow-up Visit

	Study Day																			Safety Follow-up (7 to 10 Days After Last Dose of Study Drug)
Event/Assessment[a]	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Drug test (urine or blood), including cotinine	X																			
Alcohol test (urine, blood, or breath)	X																			
Urinalysis	X							X							X					X
Spirometry[g]	X	X								X										
[redacted]																				
Study drug administration[i]: VX-445 or placebo		X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Study drug administration[i]: TEZ/IVA or placebo		X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit																			
Medications review[j]	Continuous from signing of ICF through Safety Follow-up Visit																			

CRU: clinical research unit; [redacted]; ECG: electrocardiogram; ICF: informed consent form; IVA: ivacaftor; PE: physical examination; PK: pharmacokinetic; q12h: every 12 hours; TEZ: tezacaftor

[g] On Day 1, spirometry will be performed approximately 6 hours (± 1 hour) after dosing. On Day 9, spirometry will be performed before dosing and at approximately 6 hours (± 1 hour) after dosing. The assessment on Day -1 will be performed at approximately the same time of day (± 2 hours) as the nominal time of the 6-hour postdose assessments on Days 1 and 9.

[redacted]

[i] Study drug will be administered in the fed state (see Section 9.6.1.3 of the protocol). The last dose of study drug will be administered on the morning of Day 14.

[j] All medications taken from 28 days before the first dose of study drug through the end of the study will be recorded.

Appendix B: 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 Sept 14, 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:

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

Accessed Sept 14, 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 Sept 14, 2017.

[redacted]

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX16-445-001 Version 7.0 (Final Analysis Parts D, E and F)

A Phase 1/2 Study of VX-445 in Healthy Subjects and Subjects With Cystic Fibrosis

Authors of SAP: [redacted]

Version: Version 1.0
Version Date of SAP: 15 September 2017

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

1 TABLE OF CONTENTS

2 MODIFICATIONS

2.1 Modifications to the Approved Clinical Study Protocol

- Changed the definition of Treatment-emergent Period.
- Added sensitivity analysis for $ppFEV_{1.}$

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 7.0, dated 08 Aug 2017, approved electronic case report form (eCRF) for Parts D and E, Version 1.0, dated 25 Jul 2016, and approved eCRF completion guidelines for Parts D and E, Version 1.0, dated 02 August 2017. The eCRF and eCRF completion guidelines for Part F are still in development at the time this version of SAP method is approved. 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. This SAP will be used to perform 3 IAs for Parts D, E and F separately that will occur after all subjects in each part have completed the Safety Follow-Up Visit. This SAP will also be used to perform the analysis of key study data for ongoing review by an internal limited Vertex Team.

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-445 in triple combination with TEZ/IVA and in triple combination with TEZ/VX-561 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 (SAS Institute, Cary, North Carolina, USA) 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 D and E

- To evaluate the safety and tolerability of VX-445 in TC with TEZ and IVA in subjects with CF
- To evaluate the efficacy of VX-445 in TC with TEZ and IVA in subjects with CF

Part F

- To evaluate the safety and tolerability of VX-445 in TC with TEZ and VX-561 (deuterated IVA) in subjects with CF
- To evaluate the efficacy of VX-445 in TC with TEZ and VX-561 in subjects with CF

4.2 Secondary Objectives

Parts D and E

- To evaluate the PD effect of VX-445 in TC with TEZ and IVA on CFTR function in subjects with CF
- To evaluate the PK of VX-445 when administered in TC with TEZ and IVA in subjects with CF

- To evaluate the PK of TEZ, IVA, and their respective metabolites (M1-TEZ and M1-IVA) when administered in TC with VX-445 in subjects with CF

Part F

- To evaluate the PD effect of VX-445 in TC with TEZ and VX-561 on CFTR function in subjects with CF
- To evaluate the PK of VX-445 when administered in TC with TEZ and VX-561 in subjects with CF
- To evaluate the PK of TEZ and metabolite (M1-TEZ) and VX-561 when administered in TC with VX-445 in subjects with CF

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 Day 29

5.1.2 Secondary Efficacy Endpoints

Parts D and E:

- Absolute change in sweat chloride concentrations from baseline through Day 29
- Relative change in $ppFEV_1$ from baseline through Day 29
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline at Day 29
- PK parameters of VX-445, TEZ, M1-TEZ, IVA, and M1-IVA

Part F:

- Absolute change in sweat chloride concentrations from baseline through Day 29
- Relative change in $ppFEV_1$ from baseline through Day 29
- Absolute change in CFQ-R respiratory domain score from baseline at Day 29
- PK parameters of VX-445, TEZ, M1-TEZ, and VX-561

5.2 Safety Endpoints

The safety and tolerability is evaluated via the following endpoints:

- adverse events (AEs)
- clinical laboratory values
- standard 12-lead electrocardiograms (ECGs)
- vital signs
- pulse oximetry
- spirometry

6 STUDY DESIGN

6.1 Overall Design

Part D, which is comprised of Parts D1 and D2, is randomized, double-blind, placebo-controlled and evaluates VX-445 in TC with TEZ/IVA in subjects with CF (F/MF genotypes). Part E is randomized, double-blind, TEZ/IVA-controlled and evaluates VX-445 in TC with TEZ/IVA in subjects with CF (F/F genotype). Part F is randomized, double-blind, placebo-controlled, and evaluates VX-445 in TC with TEZ/VX-561 in subjects with CF (F/MF genotypes). Part F is an optional part of the study, which will be conducted at the sponsor's discretion. All parts are multicenter and designed to evaluate the safety and efficacy of VX-445 in TC.

Approximately 104 subjects with CF will be enrolled. Part D may be initiated while Parts A, B, and C are ongoing after review of safety, tolerability, and PK data. Enrollment of Parts D1 and D2 will be sequential, while enrollment of Parts E and F will be in parallel with Part D2.

After all Part D1 subjects complete the Day 15 Visit, a blinded review of all available safety and PK data will be conducted by the Vertex study team and lead investigator(s). Dosing in Parts D2, E, and F will start after this review, if supported by safety and PK data.

Part E subjects who are participating in Study VX11-661-110 (Study 661-110), an open-label study of TEZ/IVA combination therapy, will not need to washout TEZ/IVA treatment; these subjects will transition directly from their prior treatment to the TEZ/IVA Run-in Period providing that they meet all eligibility criteria. These subjects can have screening assessments for this study done while they are continuing to participate in Study 661-110.

Key study elements are summarized in Table 6-1. The treatment arms and randomization ratios for each part are summarized in Table 6-2. A schematic of the study design is shown in Figure 6-1. Study visits and assessments are shown in Table 11-1 (Parts D1 and D2), Table 11-2 (Part E), and Table 11-3 (Part F).

Table 6-1 Parts D, E, and F: Key Study Elements

Element	Part D1	Part D2	Part E	Part F
Study population				
Genotype(s)	F/MF	F/MF	F/F	F/MF
Age	≥18 years	≥18 years	≥18 years	≥18 years
$ppFEV_1$ criteria	≥40 to ≤90	≥40 to ≤90	≥40 to ≤90	≥40 to ≤90
Number of subjects	Approximately 8	Approximately 48	Approximately 24	Approximately 24
Study design	Parallel group	Parallel group	Parallel group	Parallel group
Control	Placebo	Placebo	TEZ/IVA	Placebo

IVA: ivacaftor; MF: minimal function; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Table 6-2 Treatment Arms and Planned Doses by Part in the Treatment Period (Period 1)

Part Randomization ratio	Treatment Arm	VX-445 Dosage	TEZ Dosage	IVA Dosage	VX-561 Dosage
Part D1[a]	TC-mid	100 mg qd	100 mg qd	150 mg q12h	N/A
3:1	Triple placebo	Placebo	Placebo	Placebo	N/A
Part D2[a]	TC-high	200 mg qd	100 mg qd	150 mg q12h	N/A
6:4:3:3	TC-mid	100 mg qd	100 mg qd	150 mg q12h	N/A
	TC-low	50 mg qd	100 mg qd	150 mg q12h	N/A
	Triple placebo	Placebo	Placebo	Placebo	N/A
Part E[b]	TC-high	200 mg qd	100 mg qd	150 mg q12h	N/A
3:1	TEZ/IVA	Placebo	100 mg qd	150 mg q12h	N/A
Part F	TC2-high	200 mg qd	100 mg qd	N/A	150 mg qd[c]
3:1	Triple placebo	Placebo	Placebo	N/A	Placebo

TC2: triple combination 2 (VX-445/TEZ/VX-561); IVA: ivacaftor; N/A: not applicable; q12h: every 12 hour; qd: once daily; TC: triple combination (VX-445/TEZ/IVA); TEZ: tezacaftor

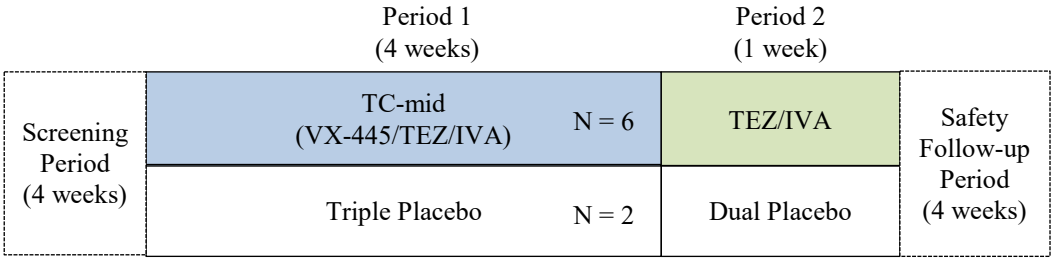
[a] In Parts D1 and D2, all subjects will also receive TEZ 100 mg qd/IVA 150 mg q12h or dual placebo during Period 2.

[b] In Part E, all subjects will also receive TEZ 100 mg qd/IVA 150 mg q12h during the Run-in Period and the Washout Period, which is the dosage evaluated in Phase 3 studies of TEZ/IVA.

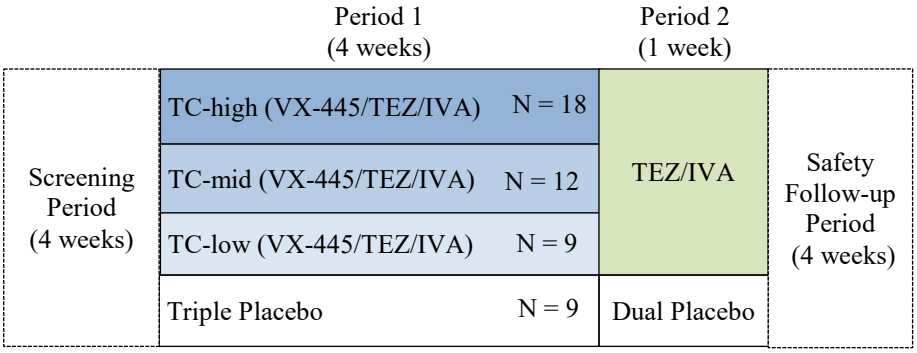
[c] See Section 9.3.2.2 of the protocol for information relating to the selection of the VX-561 dose.

Figure 6-1 Parts D, E, and F: Schematic of Study Design

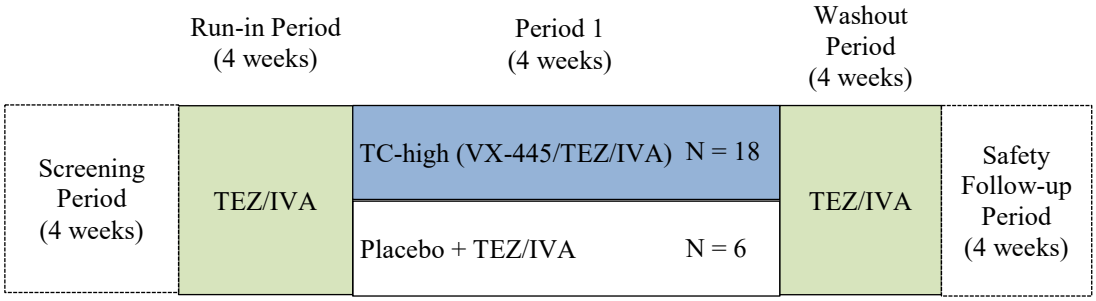
Part D1: F/MF
N ~ 8
Randomization: 3:1



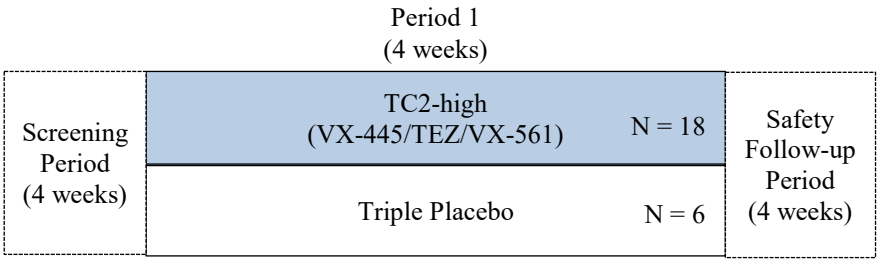
Part D2: F/MF
N ~ 48
Randomization: 6:4:3:3
Stratification: $ppFEV_1$: ≥70 versus <70



Part E: F/F
N ~ 24
Randomization: 3:1
Stratification: $ppFEV_1$: ≥70 versus <70



Part F (if Conducted): F/MF
N ~ 24
Randomization: 3:1
Stratification: $ppFEV_1$: ≥70 versus <70



TC2: triple combination 2 (VX-445/TEZ/VX-561); IVA: ivacaftor; MF: minimal function; N: number of subjects; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TC: triple combination (VX-445/TEZ/IVA); TEZ: tezacaftor
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

6.2.1.1 Primary Objectives

The primary objectives of Parts D, E, and F are the evaluation of safety and tolerability, and efficacy of VX-445 in TC with TEZ/IVA (Parts D and E) and in TC with TEZ/VX-561 (Part F) in subjects with CF. The sample size calculations described below are deemed adequate to evaluate the primary objectives, based on clinical and statistical considerations.

Safety and Tolerability

The primary safety endpoint is the incidence of AEs. Approximately 104 subjects with CF will be enrolled in the study with approximately 81 subjects receiving VX-445 in TC with either TEZ/IVA or TEZ/VX-561. The sample size for each treatment group will provide sufficient data for a descriptive analysis of AEs.

Efficacy

The primary efficacy endpoint is the absolute change from baseline in ppFEV$_1$ through Day 29 in Parts D, E, and F. A sample size of 18 subjects per treatment group provides at least 90% power to detect a mean change of 7 percentage points.

6.2.1.2 Secondary Objectives

A secondary objective of Parts D, E, and F is the evaluation of the PD effect of VX-445 in TC with TEZ/IVA (Parts D and E) and in TC with TEZ/VX-561 (Part F) in subjects with CF.

The absolute change from baseline through Day 29 in sweat chloride is a secondary endpoint used to evaluate the PD objective of the study. In Part D, 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 pre-specified that covers the range of plausible and diverse dose-response profiles.

The candidate models that best describe the expected decreasing dose-response profile of the TC groups compared to placebo include a linear model, a maximum effect (E_{max}) model, and a sigmoid E_{max} model. The contrasts (i.e., linear combinations of the treatment group means through Day 29) selected to perform the MCP and that capture the shape of these candidate models are described in Table 6-3.

Table 6-3 Contrast Coefficients for the Multiple Comparisons Procedure in Part D

Candidate Model	Placebo	TC-low	TC-mid	TC-high
Linear	3.0	1.0	-1.0	-3.0
E_{max}	3.0	-1.0	-1.0	-1.0
Sigmoid E_{max}	1.0	1.0	-1.0	-1.0

E_{max}: maximum effect; TC: triple combination (VX-445/TEZ/IVA)

A total sample size of 56 subjects in Part D will provide at least 90% power to detect a dose-response trend with MCP.

6.3 Randomization

A randomization list for each part will be produced by Vertex Biostatistics or a qualified randomization vendor. The Vertex study biostatistician will review and approve the dummy randomization list. The final randomization list will be reviewed and approved by a designated unblinded biostatistician who is not a member of the study execution team (SET).

Only subjects who have completed screening assessments and are eligible for participation in the study will be randomized to receive active study drug or placebo. Randomized subjects will be assigned a unique subject number.

For Parts D, E, and F, an interactive web response system (IWRS) will be used to assign subjects to treatment.

6.4 Blinding and Unblinding

6.4.1 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 GPS and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations
- Unblinded statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IWRS Manager
- Vertex Clinical Supply Chain
- IDMC vendor performing the interim analyses (IAs) and preparing the unblinded analysis for the ongoing reviews of efficacy and safety data, and a limited Vertex team not involved in the conduct of the study
- Bioanalytical CRO analyzing PK samples and the Vertex Bioanalytical personnel who is not a member of the SET but reviews raw data from Bioanalytical CRO. The Vertex Bioanalytical SET member will continue to be blinded.
- 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

The Vertex study team and lead investigator(s) will also conduct blinded reviews of all available safety and PK data after all subjects within a cohort complete the Day 29 Visit to make decisions about dose selection for potential subsequent cohorts.

<u>Blinding of Sweat Chloride and Spirometry Results:</u>

- The Vertex study team will not have access to the spirometry or sweat chloride results after the first dose of study drug until after the data are unblinded for full review per Section 12.3.6.1.2 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 a subject's study-related spirometry results until after the subject's last study visit, even if the subject prematurely discontinues treatment.

6.4.2 Unblinding

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

Unblinding of 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. In case of emergency, the investigator will have the final decision and unilateral right for unblinding.

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

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

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor 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 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 also 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.

Parts D, E, and F Only: Unblinded Reviews of Data by Vertex for Administrative Purposes (Planning, Decision-making, and Regulatory Submission)

A limited Vertex team not involved in the conduct of the study will be unblinded to results of the IAs and will 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

Parts D, E, and F: 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 with approval of Data Dissemination Plan before the unblinding.

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 of the Treatment Period. 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 D and F

The **Safety Set** will include all subjects who received at least 1 dose of study drug. 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 , the subject will be analyzed in the higher treatment group (in the increasing priority order: Triple placebo, TC-low, TC-mid, TC-high/TC2-high).

7.3.2 Part E

The **Safety Set for the Run-in Period** will include all subjects who received at least 1 dose of study drug 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 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, TC-high).

Note: The safety analysis will focus on the Safety Set for the Treatment Period only, thus Safety Set for Part E, implicitly, refers to Safety Set for Period 1, 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 D: F508del/MF genotypes group
    - Placebo, TC-low, TC-mid, and TC-high. The pooled TC-mid groups and the pooled placebo groups from Parts D1 and D2 will be used in all efficacy, pharmacodynamic (PD) and safety analyses for Part D.
- Part E: F508del/F508del genotype group
    - TEZ/IVA and TC-high.
- Part F: F508del/MF genotypes 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 D and F will include the time from the first dose of study drug in the Treatment Period until 28 days after the last dose of study drug or end of study date (based on end of follow-up visit in CRFs), whichever occurs first.

For Part E, 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 include the time from the first dose of study drug in the Run-in Period to: (1) the first dose 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 of study drug in the Run-in Period or end of study date (based on end of follow-up 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 include the first dose of study drug in Period 1 of the Treatment Period to 28 days after the last dose of study drug or end of study date (based on end of follow-up 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 on-treatment values, and maximum and minimum change from baseline values 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 (ppFEV1) 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 both 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 Periods 1 and 2 in Part D, the Period 1 and Washout Period in Part E, and the Period 1 in Part F 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 D and F:

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

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

- All Subjects Set (randomized or dosed)
- Randomized or dosed in the Period 1
- Randomized
- Safety Set for the Treatment Period
- Randomized but not dosed in the Period 1
- 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 (Separated by Periods 1 and 2 for Part D, and by Period 1 and washout period for Part E)
- Prematurely discontinued treatment and the reason for discontinuation (i.e., discontinued all study drugs) (Separated by Periods 1 and 2 for Part D, and by Period 1 and washout period for Part E)
- 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 E, 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 E) 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.

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 Part D1, no stratification will be performed.

  For Part D2, $ppFEV_1$ stratification (<70 versus ≥70) will be performed using the screening (Days -28 to -1) $ppFEV_1$ value.

  For Part E, $ppFEV_1$ stratification (<70 versus ≥70) will be performed using a value obtained at the following visit:

  - Screening Visit (Days -56 to -29) for subjects transitioning directly from at least 14 days of uninterrupted TEZ/IVA treatment
  - Day -14 Visit (+ 13 days) for all other subjects

  For Part F, $ppFEV_1$ stratification (<70 versus ≥70) will be performed using the screening (Days -28 to -1) $ppFEV_1$ value.

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 (WHO-DDE) and categorized as follows:

For Parts D and F:

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 E:

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 E, 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 Run-in Period, Period 1 of the Treatment Period and Washout Period for Part E, the Period 1 and Period 2 of the Treatment Period for Part D, and include the Period 1 for Part F. Further, study drug exposure for the combined Period 1 of the Treatment Period and Washout Period in Part E 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: ≤2 weeks, >2- ≤4 weeks, and > weeks (for Part D); and ≤2 weeks, >2- ≤4 weeks, >4 - ≤8 weeks, >8 weeks (Treatment and washout periods for Part E); ≤2 weeks, >2- ≤4 weeks (for Part F), 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 E, 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 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 on-treatment 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 pre-dose percent predicted FEV_1 ($ppFEV_1$ in percentage units) through Day 29 in Parts D, E and F.

The percent predicted FEV_1 is the ratio of FEV_1 (L) to the predicted FEV_1 (L), expressed as a percentage. The predicted FEV_1 will be calculated using the Quanjer GLI-2012 Regression Equations and Lookup Tables, 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 Parts D, E and F

The null hypothesis to be tested is that the mean absolute within-group change from baseline in percent predicted FEV_1 ($ppFEV_1$) through Day 29 is zero for VX-445 in triple combination (TC) with TEZ/IVA in Parts D and E, or with VX-561 in Part F, 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 D, the analysis will include 4 treatment groups: placebo, TC-low, pooled TC-mid, and TC-high. For Part E, the analysis will include 2 treatment groups: placebo + TEZ/IVA, and TC-high (VX-445/TEZ/IVA). For Part F, the analysis will include 2 treatment groups: placebo and TC2-high (VX-445/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 (Day 15 and Day 29 only) for each triple combination, 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. Day 8 data will not be included in the model for the through Day 29 analysis for Part D.

Further, the adjusted mean and 95% CI of the treatment difference between each triple combination 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.

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

8.3.1.2 Sensitivity Analysis of the Primary Efficacy Variable

If pre-dose assessment is missing and the post-dose assessment is available on Day 15, the missing record will be imputed by post-dose assessment on the same day. The sensitivity analysis of the change from baseline in $ppFEV_1$ is performed on the imputed data. The sensitivity analysis will be based on an MMRM model, similar to the primary analysis of the primary efficacy variable in Parts D, E and F. The tabular presentation of results will also be similar. The adjusted mean and 95% CI of the mean change from baseline of the average treatment effect through Day 29 will be provided along with *p*-value for all within-treatment and between-treatment comparisons, for each part, separately.

8.3.1.3 Supportive Analysis for the Primary Efficacy Variable

8.3.1.3.1 Part D: Period 2

Period 2 in Part D (after Day 29 through the Period 2 visit) will be used to assess the washout effect of VX-445 on the primary efficacy variable during the 1-week Period 2. This analysis will be based on fitting an Analysis of Covariance (ANCOVA) model to the primary efficacy variable in the Period 2, using the group as a fixed effect, and continuous baseline $ppFEV_1$ as a covariate in the ANCOVA model. Group will be assigned to placebo, TC-low, pooled TC-mid, and TC-high the 4 randomized groups in the Period 1.

The adjusted mean and 95% CI of the mean change from baseline for placebo, TC-low, pooled TC-mid, and TC-high at the Period 2 visit will be provided along with the corresponding 95% CI and *p*-value. The adjusted mean (with 95% CI) obtained from the ANCOVA analysis at Period 2 visit will be plotted by randomized group, and will be combined with the corresponding plot for the Period 1 from the primary efficacy analysis.

8.3.1.3.2 Part E: Washout Period

The Washout Period in Part E after Day 29 through Day 57 will be used to assess the washout effect of VX-445 on the primary efficacy variable during the 4-week Washout Period. This analysis will be based on fitting a fully saturated model to the primary efficacy variable in the Washout Period, using group, visit and the group-by-visit interaction effect as a fixed effect, and continuous baseline $ppFEV_1$ as a covariate in the MMRM model. Group (1 versus 2) will be assigned to the two randomized groups in the Period 1, and visit will be assigned the chronological visit within each subject. The other aspects of the MMRM model will be similar to that of the primary analysis.

The adjusted mean of the mean change from baseline for TC and TEZ/IVA at the Washout Period visits Day 43, and Day 57 will be provided along with the corresponding 95% CI and *p*-value. 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 in the Washout Period, will be used to estimate the adjusted mean at each visit in the Washout Period.

The adjusted mean (with 95% CI) obtained from the MMRM analysis at each post-baseline visit post Day 29 of the Period 1 through Day 57 of the Washout Period will be plotted by randomized

group, and combined with the corresponding plot for the Period 1 from the primary efficacy analysis.

8.3.2 Analysis of Secondary Efficacy Variables

The secondary efficacy variables include:

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

8.3.2.1 Relative change in $ppFEV_1$ from baseline through Day 29 (Parts D , E and F)

The relative change in $ppFEV_1$ from baseline through Day 29 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 Parts D, E and F. 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 (Parts D, E and F)

The absolute change in the CFQ-R respiratory domain score 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. Analysis of this variable will be based on an MMRM model, similar to the analysis of the primary efficacy variable in Parts D, E and F. Sex, the continuous baseline $ppFEV_1$, and the continuous baseline CFQ-R respiratory domain score will be used as covariates in Parts D, E and F. The presentation of results will also be similar.

Part E: Washout Period

In Part E, a supportive analysis will be based on fitting an ANCOVA model to the CFQ-R respiratory domain score Day 57 Visit during Washout Period, using the randomized group in Period 1, as a fixed effect. Sex, continuous baseline $ppFEV_1$, and continuous baseline CFQ-R respiratory domain score will be used as covariates.

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 adjusted mean (with 95% CI) obtained from the model-based analysis at each post-baseline visit will be plotted by randomized group for each part.

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

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 (Parts D, E and F)

Other efficacy variables include:

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

Only descriptive analyses will be performed.

8.3.3.1 Absolute change in CFQ-R non-respiratory domain scores from baseline at Day 29 (Parts D, E and F)

The Adolescent/Adult versions include 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.

8.3.4 Analysis of Additional Efficacy Variables (Parts D, E and F)

Other spirometry efficacy variables in parts D, E and F include:

- FEV_1:
  - Absolute change from baseline in FEV_1 (L)
  - Relative change from baseline in FEV_1 (%)
- FVC:
  - Absolute change from baseline in FVC (L)
  - Relative change from baseline in FVC (%)
  - Absolute change from baseline in percent predicted FVC (percentage points)
  - Relative change from baseline in percent predicted FVC (%)
- $FEF_{25-75\%}$:
  - Absolute change from baseline in $FEF_{25-75\%}$ (L/sec)
  - Relative change from baseline in $FEF_{25-75\%}$ (%)
  - Absolute change from baseline in percent predicted $FEF_{25-75\%}$ (percentage points)
  - Relative change from baseline in percent predicted $FEF_{25-75\%}$ (%)
- FEV_1/FVC:
  - Absolute change from baseline in FEV_1/FVC
  - Relative change from baseline in FEV_1/FVC (%)
  - Absolute change from baseline in percent predicted FEV_1/ percent predicted FVC
  - Relative change from baseline in percent predicted FEV_1/ percent predicted FVC (%)

Descriptive analyses of the change from baseline 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 pharmacodynamic (PD) effect of VX-445 in combination with TEZ/IVA (Parts D and E) and in combination with TEZ/VX-561 (Part F) 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 Day 29 (Part D)

The null hypothesis to be tested is that the dose response of the mean absolute change from baseline through Day 29 for sweat chloride is not decreasing between placebo and the 3 dose levels of VX-445 with TEZ/IVA in Part D. The test will be performed using the MCP procedure with the pre-specified contrasts provided in Section 6.2.1.2, 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 sweat chloride and continuous baseline ppFEV$_1$ as covariates, and will include all data from all treatment groups and visits through Day 29 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 Day 29 (Day 15 and Day 29 only), 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 Parts D. 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 Day 29 (Parts D, E and F)

8.3.5.2.1 Parts D, E and F

The analysis of the absolute change in sweat chloride from baseline through Day 29 will be based on an MMRM model similar to the analysis of the primary efficacy variable for Parts D, E, and F, with the continuous baseline sweat chloride and continuous baseline ppFEV$_1$ 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 Day 29 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.

8.3.5.3 Supportive Analysis for Absolute Change from Baseline in Sweat Chloride from Baseline through Day 29

Part D: Period 2

The Period 2 in Part D after Day 29 through Period 2 visit will be used to assess the washout effect of VX-445 on sweat chloride during the 1-week Period 2. This analysis will be based on fitting an Analysis of Covariance (ANCOVA) model to the absolute change from baseline in sweat chloride in the Period 2, using the group as a fixed effect, with the continuous baseline sweat chloride and baseline ppFEV1 as covariates in the ANCOVA model. Groups will be assigned to placebo, TC-low, pooled TC-mid and TC-high the 4 randomized groups in the Period 1, will be assigned within each subject.

The adjusted mean of the change from baseline for placebo, TC-low, pooled TC-mid and TC-high at the Period 2 visit will be provided along with the corresponding *p*-value.

The adjusted mean (with 95% CI) obtained from the ANCOVA analysis at Period 2 visit will be plotted by randomized group, will be combined with the corresponding plot for the Period 1 from the primary analysis of sweat chloride.

Part E: Washout Period

The Washout Period in Part E after Day 29 through Day 57 will be used to assess the washout effect of VX-445 on sweat chloride during the 4-week Washout Period. This analysis will be based on fitting a fully saturated model to the absolute change from baseline in sweat chloride in the Washout Period, using the group, visit, and group-by-visit interaction effect as a fixed effect, with the continuous baseline sweat chloride and baseline ppFEV$_1$ as covariates in the MMRM model. Group (1 versus 2) will be assigned to the two randomized groups in the Treatment Period, and visit will be assigned the chronological visit within each subject. The other aspects of the MMRM model will be similar to that of the primary analysis.

The adjusted mean and 95% CI of the mean change from baseline for TC and TEZ/IVA at the Washout Period visits Day 43 and Day 57 will be provided along with the corresponding *p*-value. Contrasts based on the fixed effects at the covariate mean of the continuous baseline sweat chloride and baseline ppFEV$_1$ for the combined treatment groups based on unique subjects in the FAS who have at least one post-baseline measurement in the Washout Period, will be used to estimate the adjusted mean at each visit in the Washout Period.

The adjusted mean (with 95% CI) obtained from the MMRM analysis at each post-baseline visit in the Washout Period will be plotted by group, combined with the corresponding plot for the Period 1 from the primary analysis of sweat chloride.

8.4 Safety Analysis

For Parts D and F, all safety analyses will be based on data from the TE Period for all subjects in the Safety Set. For Part E, all safety analyses will be based on the TE Period for the Treatment Period for all subjects in the corresponding Safety Set for 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 D and F:

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 E:

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 D and F, or the TE period for Treatment Period in Part E, 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 System Organ Class (SOC) and Preferred Term (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 D and F, or the TE period for Treatment Period for Part E, 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 aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin), a scatter plot of the maximum treatment-emergent value versus the baseline value corresponding to xULN 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 xULN 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 D and F, or the TE period for the Treatment Period in Part E, 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 . 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 D and F, or the TE period for the Treatment Period for Part E 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 D and F, or the TE period for the Treatment Period for Part E 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 percent predicted FEV_1 and change from pre-dose value for the post-dose percent predicted FEV_1 value at time point 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

Interim analyses may be performed for each part (D1, D2, E and F) after at least 50% of subjects in the part have completed the Day 15 Visit. These results will be reviewed by a limited Vertex team.

Interim analyses for Parts D, E and F separately will be performed after all subjects in each part 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.

The internal limited Vertex team data reviews will be conducted at a regular frequency during the conduct of the study.

9.1.1 Summary of the Flow of Data for Interim Analyses for each part (D1, D2 and E) at or after 50% of Subjects have Completed the Day 15 Visit

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 that may be performed after at least 50% of the subjects have completed the Day 15 visit in each part (D1, D2, E and F) and for the internal limited Vertex team data review:

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, [redacted]t, will provide the unblinded treatment codes to the unblinded Vertex Biometrics team, [redacted]
3. [redacted] provide the unblinded spirometry data to unblinded Vertex Biometrics team, [redacted] provide the unblinded sweat chloride data to unblinded Vertex Biometrics team, [redacted];
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

An independent data monitoring committee (IDMC) was formed before study initiation. The IDMC Chair reviewed available safety and PK data from Parts A, B, and C of the study prior to commencement of dosing in Part D1 to determine if it is appropriate to proceed with the study. Similarly the IDMC Chair will review available blinded safety and PK data from Part D1 prior to commencement of dosing in Part D2 to determine if it is appropriate to proceed with the rest parts of the study.

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.

LIST OF APPENDICES

Appendix A: Schedule of Assessments

Table 11-1 Study VX16-445-001: Schedule of Assessments for Parts D1 and D2

Event/Assessment[a]	Screening	Treatment Period					ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
		Period 1				Period 2		
	Days -28 to -1	Day 1[c]	Day 8 for Part D1 only (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Period 2 Visit[d]		
Informed consent	X							
Randomization[e]		X						
Demographics	X							
Medical history	X							
CFQ-R[f,g]		X		X	X			
Weight[h]	X	X	X	X	X		X	X
Height[h]	X							
Vital signs[i]	X	X	X	X	X	X	X	X
Pulse oximetry[i]	X	X	X	X	X	X	X	X

[a] All assessments will be performed before dosing, unless noted otherwise. Assessments that are collected before and after dosing 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 ETT Visit should be scheduled as soon as possible after the decision to terminate 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, and a separate Safety Follow-up Visit will not be 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 9.1.2.4 of the protocol.

[d] The Period 2 Visit will occur 6 to 10 days after the actual date of the Day 29 Visit.

[e] Randomization may occur on the previous day (Day -1 Visit) after all inclusion and exclusion criteria have been confirmed.

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

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

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

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

Table 11-1 Study VX16-445-001: Schedule of Assessments for Parts D1 and D2

Event/Assessment[a]	Screening	Treatment Period					ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
		Period 1				Period 2		
	Days -28 to -1	Day 1[c]	Day 8 for Part D1 only (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Period 2 Visit[d]		
Physical examination[j]	Complete	Abbrev.		Abbrev.	Abbrev.		Abbrev.	Complete
Standard 12-lead ECG[k]	X	X	X	X	X		X	X
Sweat chloride[g,l]	X	X	X	X	X	X[m]	X	X
Spirometry[n]	X[o]	X	X	X	X	X[m]	X	X
Urinalysis[g]	X	X	X	X	X		X	X
Pregnancy test (all females of childbearing potential)	Serum	Urine			Urine		Serum	Serum
CFTR genotype[p]	X							
FSH[q]	X							

j Complete and abbreviated PEs are described in Section 11.7.3 of the protocol. Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator or healthcare provider.

k All standard 12-lead ECGs will be performed after the subject has been seated or supine 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 all 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 Sweat chloride will be measured in all subjects as described in Section 11.4.1 of the protocol. If the value cannot be determined from the screening test, a sweat chloride value documented in a laboratory report may be used to establish eligibility. See Section 8.2.1 of the protocol (Inclusion Criterion #5) for additional detail.

m At the Period 2 Visit, sweat chloride and ppFEV$_1$ assessments should be done within 2 hours before TEZ/IVA dosing in the morning.

n Spirometry may be performed pre- or post-bronchodilator at the Screening Visit. Spirometry will be performed pre-bronchodilator, before the morning dose of study drugs, and should be performed at approximately the same time at every visit. On the Day 1 and Day 15 Visits, spirometry will also be performed 5 hours (± 1 hour) after study drug administration (pre-bronchodilator).

o For Part D2 subjects only: The ppFEV$_1$ assessment that will be used for stratification of randomization can be done any time during the Screening Period. See Section 9.1.2.2 of the protocol.

p *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. However, as outlined in Section 9.9 of the protocol subjects who have been randomized and whose screening *CFTR* genotype does not confirm study eligibility must be discontinued from the study, even if a previous *CFTR* genotype laboratory report was used to establish eligibility.

Table 11-1 Study VX16-445-001: Schedule of Assessments for Parts D1 and D2

Event/Assessment[a]	Screening	Treatment Period					ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
		Period 1				Period 2		
	Days -28 to -1	Day 1[c]	Day 8 for Part D1 only (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Period 2 Visit[d]		
G6PD activity test[r]	X							
[redacted]								
Serum chemistry and hematology[g]	X	X	X	X	X		X	X
Coagulation[g]	X	X		X	X		X	X
PK sampling[t]		X		X	X	X	X	
TEZ/IVA or placebo dosing[u]		Day 1 through Period 2 Visit						
VX-445 or placebo dosing[v]		Day 1 through Day 29						
AEs, medications[w], 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.
[redacted]
[t] Blood samples will be collected for PK analysis of VX-445, TEZ, M1-TEZ, IVA, and M1-IVA. On the Day 1 Visit, samples will be collected before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to the morning dose). On the Day 15 Visit, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing. On the Day 29 Visit, a predose sample will be collected before the morning dose of study drug. At the Period 2 Visit, a single predose sample will be collected before TEZ/IVA dosing in the morning. At the ETT Visit, a single blood sample for PK analysis will be collected.
[u] 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 TEZ/IVA or placebo in Period 2 will be the morning dose of the Period 2 Visit. See Section 9.6.2 of the protocol for additional information about study drug administration.
[v] 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-445 or placebo in Period 1 will be the morning dose on the Day 29 Visit. See Section 9.6.2 of the protocol for additional information about study drug administration.
[w] Refer to Section 9.5.2 of the protocol for details.

Table 11-1 Study VX16-445-001: Schedule of Assessments for Parts D1 and D2

	Screening	Treatment Period						
		Period 1				Period 2		
Event/Assessment[a]	**Days -28 to -1**	**Day 1**[c]	**Day 8 for Part D1 only (± 1 day)**	**Day 15 (± 2 days)**	**Day 29 (± 2 days)**	**Period 2 Visit**[d]	**ETT Visit**[b]	**Safety Follow-up 28 (± 7) Days After Last Dose**

AE: adverse event; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; *CFTR*: CF transmembrane conductance regulator gene; [redacted]; ECG: electrocardiogram; ETT: early termination of treatment; FSH: follicle-stimulating hormone; G6PD: glucose-6-phosphate dehydrogenase; ICF: informed consent form; IVA: ivacaftor; PE: physical examination; PK: pharmacokinetic; $ppFEV_1$: percent predicted forced expiratory volume in 1 second ; TEZ: tezacaftor

Table 11-2 Study VX16-445-001: Schedule of Assessments for Part E

	Screening	Run-in Period		Treatment Period: Period 1			Washout Period			Safety Follow-up
Event/Assessment[a]	Days -56 to -29	Day -28 (± 1 day)	Day -14[d] (+ 13 days)	Day 1[e]	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]
Informed consent	X									
Randomization[f]				X						
Demographics	X									
Medical history	X									
CFQ-R[g,h]				X	X	X		X		
Weight[i]	X	X		X	X	X	X	X	X	X
Height[i]	X									
Vital signs[j]	X	X		X	X	X	X	X	X	X
Pulse oximetry[j]	X	X		X	X	X	X	X	X	X
Physical examination[k]	Complete	Abbreviated		Abbreviated	Abbreviated	Abbreviated		Abbreviated	Abbreviated	Complete

[a] All assessments will be performed before dosing, unless noted otherwise. Assessments that are collected before and after dosing 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 treatment, an ETT Visit should be scheduled as soon as possible after the decision to terminate study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.
[c] Part E subjects who meet criteria specified in Section 9.1.2.6 of the protocol will not have a Safety Follow-up Visit.
[d] The Day -14 Visit is only required for subjects who are not transitioning directly from at least 14 days of uninterrupted TEZ/IVA treatment. Assessments at this visit may be performed postdose.
[e] 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 9.1.2.4 of the protocol.
[f] Randomization may occur on the previous day (Day -1 Visit) after all inclusion and exclusion criteria and criteria for entry into the Treatment Period have been confirmed. See Section 9.1.2.2.2 of the protocol.
[g] CFQ-R must be completed before the start of any other assessments scheduled at that visit.
[h] The predose assessment on the Day 1 Visit may be performed on the previous day (Day -1 Visit) if randomization has occurred.
[i] Weight and height will be measured with shoes off.
[j] Vital signs and pulse oximetry will be collected after the subject has been seated for at least 5 minutes.

Table 11-2 Study VX16-445-001: Schedule of Assessments for Part E

Event/Assessment[a]	Screening	Run-in Period		Treatment Period: Period 1			Washout Period		ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose[c]
	Days -56 to -29	Day -28 (± 1 day)	Day -14[d] (+ 13 days)	Day 1[e]	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	Day 57 (± 3 days)		
Standard 12-lead ECG[l]	X	X		X	X	X	X	X	X	X
Sweat chloride[h,m]	X		X	X	X	X	X	X	X	
Spirometry[n]	X[o]		X[o]	X	X	X	X	X	X	X
Urinalysis[h]	X	X		X	X	X	X	X	X	X
Pregnancy test (all females of childbearing potential)	Serum	Urine		Urine		Urine		Urine	Serum	Serum
CFTR genotype[p]	X									
FSH[q]	X									

[k] Complete and abbreviated PEs are described in Section 11.7.3 of the protocol. Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator or healthcare provider.

[l] All standard 12-lead ECGs will be performed after the subject has been seated or supine for at least 5 minutes. On the Days 1 and 15 Visits, ECGs will be collected before dosing and 5 hours (± 1 hour) after dosing. At all 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] Sweat chloride will be measured in all subjects as described in Section 11.4.1 of the protocol. If the value cannot be determined from the screening test (e.g. due to laboratory error), a sweat chloride value documented in a previous laboratory report may be used to establish eligibility. See Section 8.2.1 of the protocol (Inclusion Criterion #5) for additional detail.

[n] Spirometry may be performed pre- or post-bronchodilator at the Screening Visit. Spirometry will be performed pre-bronchodilator, before the morning dose of study drugs (except at the Day -14 Visit when spirometry may be performed postdose), and should be performed at approximately the same time at every visit. On the Day 1 and Day 15 Visits, spirometry will also be performed 5 hours (± 1 hour) after study drug administration (pre-bronchodilator).

[o] The ppFEV$_1$ assessment for stratification of randomization will be done at the Screening Visit for subjects transitioning directly from at least 14 days of uninterrupted TEZ/IVA treatment. For all other subjects, this assessment will be done at the Day -14 Visit. See Section 9.1.2.2 of the protocol.

[p] *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before the Day -28 Visit, a previous *CFTR* genotype laboratory report may be used to establish eligibility. However, as outlined in Section 9.9 of the protocol, subjects who have been randomized and whose screening *CFTR* genotype does not confirm study eligibility must be discontinued from the study, even if a previous *CFTR* genotype laboratory report was used to establish eligibility.

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

Table 11-2 Study VX16-445-001: Schedule of Assessments for Part E

	Screening	Run-in Period		Treatment Period: Period 1			Washout Period			
Event/Assessment[a]	**Days -56 to -29**	**Day -28 (± 1 day)**	**Day -14**[d] **(+ 13 days)**	**Day 1**[e]	**Day 15 (± 2 days)**	**Day 29 (± 2 days)**	**Day 43 (± 3 days)**	**Day 57 (± 3 days)**	**ETT Visit**[b]	**Safety Follow-up 28 (± 7) Days After Last Dose**[c]
G6PD activity test[r]	X									
[redacted]										
Serum chemistry and hematology[h]	X	X		X	X	X	X	X	X	X
Coagulation[h]	X	X		X	X	X			X	X
PK sampling[t]				X	X	X	X		X	
TEZ/IVA dosing[u]		Day -28 through Day 57								
VX-445 or placebo dosing[v]				Day 1 through Day 29						
AEs, medications[w], treatments and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit									

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

[redacted]

Blood samples will be collected for PK analysis of VX-445, TEZ, M1-TEZ, IVA, and M1-IVA. On the Day 1 Visit, samples will be collected before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to morning dose). On the Day 15 Visit, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing. On the Day 29 Visit, a predose sample will be collected before the morning dose of study drug. At the Day 43 Visit, a single blood sample for PK analysis will be collected before the morning dose of TEZ/IVA. At the ETT Visit, a single blood sample for PK analysis will be collected.

[u] The last dose of TEZ/IVA will be the morning dose on the Day 57 Visit. See Section 9.6.2 of the protocol for additional information about study drug administration.

[v] The last dose of VX-445 or placebo will be the morning dose on the Day 29 Visit. See Section 9.6.2 of the protocol for additional information about study drug administration.

[w] Refer to Section 9.5.2 of the protocol for details.

Table 11-2 Study VX16-445-001: Schedule of Assessments for Part E

Event/Assessment[a]	Screening	Run-in Period		Treatment Period: Period 1			Washout Period		ETT Visit[b]	Safety Follow-up
	Days -56 to -29	Day -28 (± 1 day)	Day -14[d] (+ 13 days)	Day 1[e]	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	Day 57 (± 3 days)		28 (± 7) Days After Last Dose[c]

AE: adverse event; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; *CFTR*: CF transmembrane conductance regulator gene; [redacted]; ECG: electrocardiogram; ETT: early termination of treatment; FSH: follicle-stimulating hormone; G6PD: glucose-6-phosphate dehydrogenase; ICF: informed consent form; IVA: ivacaftor; PE: physical examination; PK: pharmacokinetic; $ppFEV_1$: percent predicted forced expiratory volume in 1 second ; TEZ: tezacaftor

Table 11-3 Study VX16-445-001: Schedule of Assessments for Part F (if Conducted)

Event/Assessment[a]	Screening	Treatment Period: Period 1				ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
	Days -28 to -1	Day 1[c]	Day 8[d] (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)		
Informed consent	X						
Randomization[e]		X					
Demographics	X						
Medical history	X						
CFQ-R[f,g]		X		X	X		
Weight[h]	X	X		X	X	X	X
Height[h]	X						
Vital signs[i]	X	X		X	X	X	X
Pulse oximetry[i]	X	X		X	X	X	X

[a] All assessments will be performed before dosing, unless noted otherwise. Assessments that are collected before and after dosing 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 ETT Visit should be scheduled as soon as possible after the decision to terminate 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, and a separate Safety Follow-up Visit will not be 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 9.1.2.4 of the protocol.

[d] The laboratory assessment may be collected at the clinic, at a local laboratory, or during a visit by a qualified individual (e.g., home nurse). If the laboratory assessment is not collected at the clinic, a telephone call to the clinic is required for the collection of AEs. When the laboratory assessment is done in the clinic, the AE collection will also occur in the clinic.

[e] Randomization may occur on the previous day (Day -1 Visit) after all inclusion and exclusion criteria have been confirmed.

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

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

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

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

Table 11-3 Study VX16-445-001: Schedule of Assessments for Part F (if Conducted)

Event/Assessment[a]	Screening	Treatment Period: Period 1				ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
	Days -28 to -1	Day 1[c]	Day 8[d] (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)		
Physical examination[j]	Complete	Abbrev.		Abbrev.	Abbrev.	Abbrev.	Complete
Standard 12-lead ECG[k]	X	X		X	X	X	X
Sweat chloride[g,l,]	X	X		X	X	X	X
Spirometry[m]	X[n]	X		X	X	X	X
Urinalysis[g]	X	X		X	X	X	X
Pregnancy test (all females of childbearing potential)	Serum	Urine			Urine	Serum	Serum
CFTR genotype[o]	X						
FSH[p]	X						
G6PD activity test[q]	X						

j Complete and abbreviated PEs are described in Section 11.7.3 of the protocol. Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator or healthcare provider.

k All standard 12-lead ECGs will be performed after the subject has been seated or supine 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 all 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 Sweat chloride will be measured in all subjects as described in Section 11.4.1 of the protocol. If the value cannot be determined from the screening test, a sweat chloride value documented in a previous laboratory report may be used to establish eligibility. See Section 8.2.1 of the protocol (Inclusion Criterion #5) for additional detail.

m Spirometry may be performed pre- or post-bronchodilator at the Screening Visit. Spirometry will be performed pre-bronchodilator, before the morning 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 pre-bronchodilator, 5 hours (± 1 hour) after study drug administration.

n The ppFEV$_1$ assessment that will be used for stratification of randomization can be done any time during the Screening Period. See Section 9.1.2.2 of the protocol.

o *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. However, as outlined in Section 9.9 of the protocol, subjects who have been randomized and whose screening *CFTR* genotype does not confirm study eligibility must be discontinued from the study, even if a previous *CFTR* genotype laboratory report was used to establish eligibility.

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

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

Table 11-3 Study VX16-445-001: Schedule of Assessments for Part F (if Conducted)

Event/Assessment[a]	Screening	Treatment Period: Period 1				ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
	Days -28 to -1	Day 1[c]	Day 8[d] (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)		
[redacted]							
Serum chemistry and hematology[g]	X	X	X	X	X	X	X
Coagulation[g]	X	X		X	X	X	X
PK sampling[s]		X		X	X	X	
VX-445/TEZ/VX-561 or placebo dosing[t]		Day 1 through Day 29					
AEs, medications[u], treatments, and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit						

AE: adverse event; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; *CFTR*: CF transmembrane conductance regulator gene; [redacted]; ECG: electrocardiogram; ETT: early termination of treatment; FSH: follicle-stimulating hormone; G6PD: glucose-6-phosphate dehydrogenase; ICF: informed consent form; IVA: ivacaftor; PE: physical examination; PK: pharmacokinetic; $ppFEV_1$: percent predicted forced expiratory volume in 1 second ; TEZ: tezacaftor

[redacted]

Blood samples will be collected for PK analysis of VX-445, TEZ, M1-TEZ, and VX-561. On the Day 1 Visit, samples will be collected before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to the morning dose). On the Day 15 Visit, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing. On the Day 29 Visit, a predose sample will be collected before the morning dose of study drug. At the ETT visit, a single blood sample for PK analysis will be collected.

t 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-445/TEZ/VX-561 or placebo will be the morning dose on the Day 29 Visit. See Section 9.6.2 of the protocol for additional information about study drug administration.

u Refer to Section 9.5.2 of the protocol 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 (Parts D1 and D2)			
Serum Chemistry Hematology Weight	Day 1 (Baseline) Day 8 (Part D1) Day 15(Part D1) Day 15(Part D2) Day 29 Safety Follow-up	1 8 15 15 29 64	≤1 Pre-dose [1, 12] Day 1 post dose (12, 22] [1, 22] Day 1 post dose (22, 47] Use nominal visit
Coagulation	Day 1 (Baseline) Day 15 Day 29 Safety Follow-up	1 15 29 64	≤1 Pre-dose [1, 22] Day 1 post dose (22, 47] Use nominal visit
Vital Signs Pulse Oximetry	Day 1 (Baseline) Day 8 (Part D1) Day 15(Part D1) Day 15(Part D2) Day 29 Period 2 visit Safety Follow-up	1 8 15 15 29 Period 2 visit (36) 64	≤1 Pre-dose [1, 12] (12,22] [1, 22] (22, 33] (33, 50] Use nominal visit
Standard 12-Lead ECG	Day 1 (Baseline; before dosing) Day 1 (5 hours after dosing) Day 8 (Part D1 only) Day 15 (before dosing and 5 hours after dosing) Day 29 Safety Follow-up	1 1 8 15 29 64	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 E)			
Serum Chemistry Hematology Vital Signs (including Weight) Pulse Oximetry	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] Day 1 post dose (22, 36] (36, 50] (50, 71] Use nominal visit

[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 Spirometry measurements.

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

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)
Coagulation	Day 1 (Baseline) Day 15 Day 29 Safety Follow-up	1 15 29 85	≤1 Pre-dose [1,22] Day 1 post dose (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
Spirometry	Day 1 (5 hours post dose) Day 15 (5 hours post dose)	1 15	Use nominal visit Use nominal visit
Safety Assessment (Part F)			
Serum Chemistry Hematology	Day 1 (Baseline) Day 8 Day 15 Day 29 Safety Follow-up	1 8 15 29 57	≤1 Pre-dose [1, 12] Day 1 post dose (12,22] (22, 43] Use nominal visit
Coagulation Vital Signs (including Weight) Pulse oximetry	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 (Parts D1 and D2)			
Spirometry Sweat Chloride	Day 1 (Baseline) Day 8 (Part D1) Day 15 (Part D1) Day 15 (Part D2) Day 29 Period 2 visit Safety Follow-up	1 8 15 15 29 Period 2 visit (36) 64	≤1 Pre-dose (1, 12] (12, 22] (1, 22] (22, 33] (33, 50] Use nominal visit
CFQR	Day 1 (Baseline) Day 15 Day 29	1 15 29	≤1 Pre-dose (1, 22] (22, 47]
Efficacy Assessment (Part E)			

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 (Baseline)	1	≤1 Pre-dose
	Day 15	15	(1,22]
	Day 29	29	(22, 36]
	Day 43	43	(36, 50]
	Day 57	57	(50, 71]
	Safety Follow-up	85	Use nominal visit
Sweat Chloride	Day 1 (Baseline)	1	≤1 Pre-dose
	Day 15	15	(1,22]
	Day 29	29	(22, 36]
	Day 43	43	(36, 50]
	Day 57	57	(50, 71]
CFQR	Day 1 (Baseline)	1	≤1 Pre-dose
	Day 15	15	(1,22]
	Day 29	29	(22, 43]
	Day 57	57	(43, 71]
Efficacy Assessment (Part F)			
Spirometry Sweat Chloride	Day 1 (Baseline)	1	≤1 Pre-dose
	Day 15	15	(1,22]
	Day 29	29	(22, 43]
	Safety Follow-up	57	Use nominal visit
CFQR	Day 1 (Baseline)	1	≤1 Pre-dose
	Day 15	15	(1,22]
	Day 29	29	(22, 43]

Notes:
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 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 times of 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.

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

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study 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 cannot be determine in which period the interruption occurred, then assume the interruption occurred during the Period 1 for 1 day.

5. Sweat Chloride:

The qualified left arm and right arm sweat chloride assessments on Day 1 with the 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 D and F

	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 E

	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

Important protocol deviations before first dose

Stratification error based on comparing the IWRS stratification with the clinical database

For Part D2, $ppFEV_1$ stratification (<70 versus ≥70) will be performed using the screening (Days -28 to -1) $ppFEV_1$ value.

For Part E, $ppFEV_1$ stratification (<70 versus ≥70) will be performed using a value obtained at the following visit:

- Screening Visit (Days -56 to -29) for subjects transitioning directly from at least 14 days of uninterrupted TEZ/IVA treatment
- Day -14 Visit (+ 13 days) for all other subjects

For Part F, ppFEV1 stratification (<70 versus ≥70) will be performed using the screening (Days -28 to -1) ppFEV-1 value.

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 Sept 14, 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:

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

Accessed Sept 14, 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 Sept 14, 2017.

Data handling rule for spirometry is as follows:

- Input age and height with at least 2 decimal places.
- 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 coefficients 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.

Appendix G: Imputation Rules for Missing AE dates

H.1 Parts D1, D2 and F

Imputation rules for missing or partial AE start date for Parts D1, D2 and F 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 E

Imputation rules for missing or partial AE start date for Part E 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 (PPT)	>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	Per HV grade 2, 3, plus shift change
	<50 bpm	
	<45 bpm	
	Decrease from baseline ≥10 bpm	
	Decrease from baseline ≥20 bpm	
	<50 bpm and decrease from baseline ≥10 bpm	
	<50 bpm and decrease from baseline ≥20 bpm	
	Tachycardia	Per HV grade 1, 2, 3, plus shift change
	>100 bpm	
	>115 bpm	
	>130 bpm	
	Increase from baseline ≥10 bpm	
	Increase from baseline ≥20 bpm	
	>100 bpm and increase from baseline ≥10 bpm	
	>100 bpm and increase from baseline ≥20 bpm	
PR	≥240 ms	
	≥300 ms	
	≥200 ms and increase from baseline ≥40 ms	
	≥200 ms and increase from baseline ≥100 ms	
QRS	>110 ms	
	>160 ms	
	Increase from baseline ≥20 ms	
	Increase from baseline ≥40 ms	
QTc		To be applied to any kind of QT correction formula.
Borderline	>450 ms (Male) and <500ms; >470 ms and <500ms (Female)	
Prolonged*	≥500 ms	
Additional	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
HR	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	
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	

Table 11-10 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
DBP increased		
	>90 mmHg	
	>100 mmHg	
	>5 mmHg increase from baseline	
	>10 mmHg increase from baseline	
	>90 mmHg and >5 mmHg increase from baseline	
	>90 mmHg and >10 mmHg increase from baseline	
	>100 mmHg and >5 mmHg increase from baseline	
	>100 mmHg and >10 mmHg increase from baseline	
DBP decreased		
	<60 mmHg	
	<45 mmHg	
	>5 mmHg decrease from baseline	
	>10 mmHg decrease from baseline	
	<60 mmHg and >5 mmHg decrease from baseline	
	<60 mmHg and >10 mmHg decrease from baseline	
	<45 mmHg and >5 mmHg decrease from baseline	
	<45 mmHg and >10 mmHg decrease from baseline	
Weight	Weight gain	CTCAE grade 1-3
	≥5 % increase from baseline	
	≥10 % increase from baseline	
	≥ 20% increase from baseline	
	Weight loss	CTCAE grade 1-3
	≥5 % decrease from baseline	
	≥10 % decrease from baseline	
	≥ 20% decrease from baseline	