# 1 TITLE PAGE

*VERTEX PHARMACEUTICALS INCORPORATED*

# Clinical Study Protocol

**Phase 3b, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Safety, Efficacy, and Tolerability of Tezacaftor/Ivacaftor (TEZ/IVA) in an Orkambi-experienced Population Who Are Homozygous for the *F508del-CFTR* Mutation**

**Vertex Study Number: VX16-661-114**

[redacted]

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# 2 PROTOCOL SYNOPSIS

**Title** Phase 3b, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Safety, Efficacy, and Tolerability of Tezacaftor/Ivacaftor (TEZ/IVA) in an Orkambi-experienced Population Who Are Homozygous for the *F508del-CFTR* Mutation

**Brief Title** A Study to Evaluate Safety, Efficacy, and Tolerability of TEZ/IVA in Subjects With Cystic Fibrosis (CF) Who Have Previously Discontinued Orkambi

**Clinical Phase and Clinical Study Type** Phase 3b

**Objectives**

**Primary**

- To evaluate the respiratory safety of TEZ/IVA in subjects with CF homozygous for *F508del* and who discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment

**Secondary**

- To evaluate the efficacy of tezacaftor in combination with ivacaftor (TEZ/IVA) in subjects with CF homozygous for *F508del* and who discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment.
- To evaluate patient-reported outcomes after treatment with TEZ/IVA in subjects with CF homozygous for *F508del* who discontinued with Orkambi due to respiratory symptoms considered related to treatment.

**Endpoints**

**Primary**

- Incidence of respiratory adverse events (AEs)

**Key Secondary**

- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline to the average of the Day 28 and Day 56 measurements.

**Secondary**

- Relative change in $ppFEV_1$ from baseline to the average of the Day 28 and Day 56 measurements.
- Absolute change in Cystic Fibrosis Questionnaire Revised (CFQ-R) respiratory domain score from baseline to the average of the Day 28 and Day 56 measurements
- Tolerability based on study drug discontinuation through Day 56
- Safety assessments based on AEs, clinical laboratory values (hematology, serum chemistry, coagulation studies, and urinalysis), vital signs, pulse oximetry, and postdose spirometry

**Number of Subjects** Approximately 90 (45 per arm)

**Study Population** Male and female subjects aged 12 years or older with CF who are homozygous for the *F508del- Cystic Fibrosis transmembrane conductance regulator (CFTR)* mutation and who have previously discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment.

**Investigational Drug**

**Active substance:** TEZ and IVA

**Activity:** CFTR corrector and potentiator (increased chloride ion [$Cl^-$] secretion)

**Strength and Route of Administration:** TEZ 100-mg/IVA 150-mg fixed-dose combination (light yellow) film-coated tablet for oral administration

**Active substance:** IVA

**Activity:** CFTR potentiator (increased $Cl^-$ secretion)

**Strength and Route of Administration:** IVA 150-mg (light blue) film-coated tablet for oral administration

**Active substance:** not applicable

**Activity:** placebo

**Strength and Route of Administration:** 0 mg film-coated matching placebo tablets for oral administration

**Study Duration**

Excluding the Screening Period, each subject will participate in the study for 84 (± 3) days (from Day 1 through last day of Safety Follow-up Contact).

**Study Design**

This study includes the following:

- Screening Period (Day −28 through Day −1)
- Treatment Period (Day 1 through Day 56 ± 5 days)
- Safety Follow-up Contact (28 days ± 7 days after the last dose of study drug)

Subjects will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), sex (male versus female), and $ppFEV_1$ severity determined during the Screening Visit (<40% versus ≥40% predicted), and then randomized (1:1) to 1 of the following 2 treatment arms:

**TEZ/IVA**: TEZ 100 mg once daily (qd) + IVA 150 mg every 12 hours (q12h)

**Placebo**: Placebo regimen with visually matched tablets

Subjects who complete the Day 56 Visit will be offered the opportunity to receive TEZ/IVA through the Expanded Access Program if they meet the eligibility criteria for that program.

**Schedule of Study Visits**

**Screening Period:**

After obtaining consent and assent (where applicable), screening evaluations will be completed at any time during a period of 28 days (Day -28 through Day -1) before the first dose of the study drug.

**Treatment Period**:

The first dose of the study drug will be administered on Day 1 and after randomization. Clinic visits will occur on Day 1, Day 15 (± 3 days), and at Day 28 and Day 56 (± 5 days).

**Safety Follow-up Contact:**

A Safety Follow-up Contact will be performed 28 days (±7 days) after the last dose of study drug. The Safety Follow-up Contact may be a telephone interview; however, if deemed necessary by the investigator, a Safety Follow-up Visit may be required with necessary assessments to be determined by the investigator.

**Assessments**

**Safety:** AEs, clinical laboratory assessments (i.e., hematology, serum chemistry, coagulation studies, and urinalysis), vital signs, physical examinations, ophthalmologic examinations, pulse oximetry, and postdose spirometry (Day 1 only).

**Efficacy:** Spirometry and CFQ-R

**Tolerability:** discontinuation of study drug

**Statistical Analyses**

**Sample Size Consideration**

Sample size calculation is based on the key secondary endpoint of absolute change in $ppFEV_1$ from baseline to the average of the Day 28 and Day 56 measurements.

A Bayesian approach will be used to assess the treatment effect on the change in $ppFEV_1$. The study will be considered successful if the posterior probability that the treatment difference between TEZ/IVA and placebo is greater than 0 is at least 80%, using a noninformative prior distribution. Assuming a 3.0 percentage points mean treatment difference between TEZ/IVA and placebo and a standard deviation (SD) of 6.0 percentage points, with 42 TEZ/IVA subjects and 42 placebo subjects, the Bayesian power to achieve the posterior probability criterion is at least 90% (92.6%). After adjusting for an assumed dropout rate of 5% a total sample size of 90 subjects is needed.

**Analyses Sets**

The Full Analysis Set (FAS) is defined as all randomized subjects who have received at least 1 dose of study drug. The FAS will be used in efficacy analyses in which subjects will be analyzed according to their randomized treatment group.

The Safety Set is defined as all subjects who received at least 1 dose of study drug. The Safety Set is to be used for all safety and tolerability analyses, in which subjects will be analyzed according to the treatment they received.

**Safety Analyses**

Respiratory safety of TEZ/IVA is the primary objective of this study and will be assessed in terms of AE incidence, including but not limited to the following:

- Chest discomfort
- Dyspnea (shortness of breath)
- Respiration abnormal (chest tightness)
- Asthma
- Bronchial hyperreactivity
- Bronchospasm
- Wheezing

All safety analyses will be based on the TE Period for subjects in the Safety Set.
The overall safety profile of study treatments will be assessed in terms of the following safety endpoints:

- Incidence of treatment-emergent adverse events (TEAEs), SAEs, and discontinuations due to AEs
- Clinical laboratory values
- Vital signs
- Pulse oximetry

All safety data will be listed by subject in data listings.

Summaries of TEAEs will be presented by MedDRA system organ class and preferred term.

**Efficacy Analysis**

The actual posterior/conditional probability will be calculated for the probability of a greater than zero (>0) treatment effect difference in mean $ppFEV_1$ change between TEZ/IVA and placebo is greater than or equal to 80%, based on the observed data of the efficacy endpoint on the absolute change from baseline in $ppFEV_1$ to the average of the Day 28 and Day 56 measurements. This will serve as the primary efficacy analysis outcome.

Additionally, the key efficacy endpoint of the absolute change from baseline in $ppFEV_1$ to the average of the Day 28 and Day 56 measurements will be analyzed using a mixed-

effects model for repeated measures (MMRM) with $ppFEV_1$ at each time point as the outcome variable. The MMRM model will include the absolute change from baseline in $ppFEV_1$ at each visit as the dependent variable; treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect, with adjustment for sex (male versus female), age group at the Screening Visit (<18 versus ≥18 years old), and $ppFEV_1$ severity determined during the Screening (or baseline) Period (<40% versus ≥40% predicted).

The estimated treatment effect within TEZ/IVA and placebo arm, as well as the estimated treatment difference between TEZ/IVA and placebo arm will be provided based on the MMRM model along with 95% confidence interval (CI). These results will serve as additional efficacy outcomes, which is in addition to the primary actual posterior/conditional probability outcome. Furthermore, treatment effect and treatment difference at each post-baseline visit, obtained from the model, will also be provided.

Secondary endpoints including relative change of $ppFEV_1$, CFQ-R respiratory domain score will be analyzed in a similar fashion as the analysis for the primary endpoint.

**Tolerability Analysis**

A tolerability analysis will be based on the Safety Set for a standard summary of study drug discontinuation rate. Rate will be reported as descriptive statistics in percentages and no statistical hypothesis testing will be performed.

**IDMC Reviews**

The independent data monitoring committee (IDMC) will conduct regular planned safety reviews of study data as outlined in the IDMC Charter.

# 3 SCHEDULE OF ASSESSMENTS

Schedules of Assessments are shown in Table 3-1 and Table 3-2.

All visits are to be scheduled relative to the Day 1 Visit (first dose of study drug).

**Table 3-1 Study VX16-661-114: Screening**

| Event/Assessment | Screening Visit Day -28 to Day -1 |
|---|---|
| Informed consent and assent (when applicable) | X |
| Demographics | X |
| Medical history | X |
| *CFTR* genotype[a] | X |
| Ophthalmologic examination[b] | X |
| Prior and concomitant medications[c] | X |
| Height and weight (measured with shoes off) | X |
| Vital signs[d] | X |
| Pulse oximetry[d] | X |
| Physical examination of all body systems | X |
| Serum FSH[e] (amenorrheic female subjects only) | X |
| Serum pregnancy test[f] | X |
| Safety labs[g] | X |
| Spirometry[h] | X |
| Inclusion/exclusion criteria review | X |
| AEs and SAEs | Continuous from signing of informed consent form (ICF) and assent (where applicable) through Safety Follow-up Contact |

AE: adverse event; CFTR: cystic fibrosis transmembrane conductance regulator;; FSH: follicle-stimulating hormone; ICF: informed consent form; SAE: serious adverse event

[a] Only if the *CFTR* genotype is not documented in the subject's medical record.

[b] An ophthalmologic examination is required for subjects <18 years who did not have an ophthalmologic examination prior to starting Orkambi if they have not have one within 6 months before the Screening Period. Subjects who have documentation of bilateral lens removal do not need an ophthalmologic examination (Section 11.4.7).

[c] All medications taken within 28 days before the Screening Period through the end of the study will be recorded.

[d] Vital signs (pulse rate, blood pressure, and respiration rate) and pulse oximetry will be collected after the subject has been at rest in the seated or supine position for at least 5 minutes.

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

[f] Any female subject who does not meet the criteria for non-childbearing potential is considered to be of childbearing potential and must have a serum pregnancy test. (Section 11.4.4.1)

[g] Includes serum chemistry, hematology, coagulation, and urinalysis.

[h] Spirometry may be performed pre- or post-bronchodilator (Section 11.3.1). Screening spirometry evaluation may be repeated, as specified in Section 9.1.1.1.

**Table 3-2 Study VX16-661-114: Treatment Period, ETT, and Safety Follow-up Contact Assessments**

| Event/Assessment[a] | Day 1 | Day 3 Telephone Contact[b] | Day 15 (± 3 Days) | Day 28 (± 5 Days) | Day 56 (± 5 Days) | Early Termination of Treatment[c] | Safety Follow-up Contact 28 (± 7) Days After Last Dose of Study Drug[d] |
|---|---|---|---|---|---|---|---|
| Inclusion and exclusion criteria review | X | | X | X | X | | |
| Randomization[e] | X | | | | | | |
| Clinic visit | X | | X | X | X | X | |
| CFQ-R[f] | X | | X | X | X | X | |
| Spirometry[g] | X | | X | X | X | X | |
| Height (<18 years old only) | X | | X | X | X | X | |
| Vital signs[h] | X | | X | X | X | X | |
| Pulse oximetry[h] | X | | X | X | X | X | |
| Physical examination[i] | X | | | | | X | |
| Pregnancy test | urine | | urine | urine | serum | serum | |
| Safety labs[j] | X | | X | | X | X | |
| Snack or meal at site[k] | X | | X | X | X | | |
| Study drug dosing[l] | X | | X | X | X | | |
| Study drug count | X | | X | X | X | X | |
| Concomitant medications | X | | X | X | X | X | X |
| Concomitant treatment and procedures review | X | | X | X | X | X | X |
| AEs and SAEs | Continuous from signing of the ICF and assent (where applicable) through the Safety Follow-up Contact[m] | | | | | | |

[a] All assessments will be performed before dosing unless noted otherwise

[b] On Day 3, there is a telephone contact to collect AEs.

[c] If the subject prematurely discontinues study drug treatment, an ETT Visit should be scheduled as soon as possible after the decision to terminate study treatment. Subjects who prematurely discontinue study drug treatment will also be required to complete the Safety Follow-up Contact, approximately 28 (± 7) days after their last dose of study drug. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Contact, and a separate Safety Follow-up Contact will not be required. See Section 9.1.4.

[d] Telephone contact may be acceptable. A clinic visit may be required at the discretion of the investigator (Section 9.1.3).

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

[f] The CFQ-R must be completed as the first assessment at each visit.

[g] Predose spirometry must be performed before dosing and should be performed prebronchodilator at all visits. Postdose spirometry will be performed at 2 hours (± 30 minutes) and 4 hours (± 30 minutes) after dosing on Day 1 only.

[h] Vital signs (pulse rate, blood pressure, and respiration rate) and pulse oximetry will be collected after the subject has been at rest in the seated or supine position for at least 5 minutes. Vital signs and pulse oximetry will be collected predose at all visits.

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

[j] Includes serum chemistry, hematology, coagulation and urinalysis.

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

[l] On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed.

[m] For enrolled subjects who do not have a Safety Follow-up Contact, AEs and SAEs will be collected through the earliest of either 28 days after the last dose of study drug, or the ETT Visit (if that visit is 3 weeks or later following the last dose of study drug; see Section 9.1.4).

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## List of Tables



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## List of Abbreviations

| Abbreviation | Term |
|---|---|
| AE | adverse event |
| ALT | alanine transferase |
| AST | aspartate transaminase |
| ATS | American Thoracic Society |
| CF | cystic fibrosis |
| CFQ-R | Cystic Fibrosis Questionnaire-Revised |
| *CFTR* | CF transmembrane conductance regulator gene |
| CI | confidence interval |
| $Cl^-$ | chloride ion |
| CRF | case report form |
| CRO | contract research organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | cytochrome P450 |
| EDC | electronic data capture |
| ERS | European Respiratory Society |
| ETT | early termination of treatment |
| F508del | CFTR protein lacking the phenylalanine normally found at position 508 of the wild-type protein |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| $FEV_1$ | forced expiratory volume in 1 second |
| FSH | follicle-stimulating hormone |
| FVC | forced vital capacity |
| GCP | Good Clinical Practice |
| GPS | Global Patient Safety |
| [redacted] | [redacted] |
| ICF | informed consent form |
| ICH | International Council on Harmonization |
| IDMC | independent data monitoring committee |
| IEC | independent ethics committee |
| IRB | institutional review board |
| IVA | ivacaftor |
| IWRS | interactive web response system |
| LFT | liver function test |
| LUM | lumacaftor |
| MedDRA | Medical Dictionary for Regulatory Activities |
| min | minutes |
| MMRM | mixed-effects model for repeated measures |
| PAP | pulmonary arterial pressure |
| PE | physical examination |
| $ppFEV_1$ | percent predicted forced expiratory volume in 1 second |
| q12h | every 12 hours |

| Abbreviation | Term |
|---|---|
| qd | daily |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| TEAE | treatment-emergent adverse event |
| TEZ | tezacaftor |
| TEZ/IVA | tezacaftor in combination with ivacaftor |
| ULN | upper limit of normal |

# 5 INTRODUCTION

Cystic fibrosis (CF) affects more than 70,000 children and adults worldwide[1] and is the most common fatal genetic disease in persons of European descent.[2] CF is caused by a defect in the gene encoding the CF transmembrane conductance regulator (CFTR), an ion channel that regulates the flow of chloride and other ions in epithelia of various tissues, including lungs, pancreas and other gastrointestinal organs, and sweat glands. Decreased CFTR activity in people with CF results in multisystem pathology[3], beginning at birth. Despite progress in the treatment of CF with antibiotics and mucolytics, the median predicted survival age for a person with CF is approximately 40 years.[4] More effective treatments are needed for CF.

To address this medical need, Vertex Pharmaceuticals Incorporated is developing treatment regimens that include CFTR modulators to target the underlying cause of CF: the defective CFTR protein. Two types of CFTR modulators have been developed: potentiators, which increase the channel gating activity of the CFTR protein, and correctors, which increase the quantity of CFTR at the cell surface. Potentiators can increase the activity of CFTR protein delivered to the cell surface by correctors: therefore, CFTR potentiators and correctors are complementary therapeutic approaches.

Ivacaftor (IVA; Kalydeco®), the first CFTR modulator developed by Vertex, is an orally administered CFTR potentiator that increases the channel-open probability of CFTR protein to enhance chloride transport. Globally, Kalydeco is indicated for the treatment of CF in patients as young as 2 years who have the *G551D* and certain other gating mutations as well as the *R117H* mutation in the *CFTR* gene depending on the country. [5]

Lumacaftor (LUM), the second CFTR modulator developed by Vertex, is a CFTR-specific corrector that increases the delivery of CFTR protein at the cell surface by improving the processing and trafficking of the CFTR protein.

Orkambi® is a fixed-dose combination pill of LUM/IVA, which increases the quantity and function of the CFTR protein at the cell surface. It is indicated for the treatment of CF in patients as young as 6 years and older who are homozygous for *F508del*.

In clinical trials, LUM/IVA therapy significantly improved lung function and other measures of disease and reduced the rate of pulmonary exacerbations in patients with CF who were homozygous for *F508del*. However, in Phase 1 studies with healthy subjects, there was a decline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) observed within 4 hours of dosing LUM/IVA. Postdose spirometry was not done in Phase 3 studies with LUM/IVA, but the incidence of respiratory symptoms (i.e., chest discomfort, dyspnea, and respiration abnormal) was 22.0% in subjects who received the commercialized dose of the LUM/IVA and 13.8% in subjects who received placebo. Post-marketing data for Orkambi suggests that patients have discontinued treatment due to respiratory events. Therefore, there is an unmet medical need for treatment of patients homozygous for *F508del* and who have discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment.

Tezacaftor (TEZ) is a CFTR corrector being developed by Vertex that is being evaluated in several ongoing Phase 3 studies. Phase 2 data indicate that TEZ in combination with IVA (TEZ/IVA) showed statistically significant improvements in lung function ($ppFEV_1$) in subjects with CF who have at least 1 copy of *F508del* after 28 days of treatment. In

Studies VX11-661-101 (Study 101) and VX15-661-103, no trends in respiratory events were observed for subjects who received TEZ (alone or in combination with IVA). In addition, the independent data monitoring committee (IDMC) for the Phase 3 program has not identified any meaningful trends in postdose spirometry or adverse event (AE) data to suggest that TEZ/IVA is associated with respiratory symptoms. Because there is no association of respiratory events with TEZ/IVA, it is reasonable to hypothesize that TEZ/IVA may be a treatment for patients who have discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment.

# 6 STUDY OBJECTIVES

## 6.1 Primary Objective(s)

- To evaluate the respiratory safety of TEZ/IVA in subjects with CF homozygous for *F508del* and who discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment.

## 6.2 Secondary Objective(s)

- To evaluate the efficacy of TEZ/IVA in subjects with CF homozygous for the *F508del-CFTR* mutation and who discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment.
- To evaluate patient-reported outcomes after treatment with TEZ/IVA in subjects with CF homozygous for the *F508del-CFTR* mutation and who discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment.

# 7 STUDY ENDPOINTS

## 7.1 Primary Endpoint

- Incidence of respiratory AEs

## 7.2 Key Secondary Endpoint

- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline to the average of the Day 28 and Day 56 measurements.

## 7.3 Secondary Endpoints

- Relative change in $ppFEV_1$ from baseline to the average of the Day 28 and Day 56 measurements.
- Absolute change in Cystic Fibrosis Questionnaire Revised (CFQ-R) respiratory domain score from baseline to the average of the Day 28 and Day 56 measurements.
- Tolerability based on discontinuation of TEZ/IVA through Day 56
- Safety assessments based on AEs, clinical laboratory values (hematology, serum chemistry, coagulation studies, and urinalysis), vital signs, pulse oximetry, and postdose spirometry

# 8 STUDY POPULATION

Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are enrolled.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for the study.

## 8.1 Inclusion Criteria

1. Subject (or subject's legally appointed and authorized representative) will sign and date an informed consent form (ICF) and, where appropriate, an assent form.

2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.

3. Males or females, aged 12 years or older on the date of informed consent or, where appropriate, date of assent.

4. Prior discontinuation of Orkambi, with at least 1 respiratory sign or symptom considered related to therapy, including but not limited to the following:

- Chest discomfort
- Dyspnea (shortness of breath)
- Respiration abnormal (chest tightness)
- Asthma
- Bronchial hyperreactivity
- Bronchospasm
- Wheezing
- Asymptomatic reduction in relative change in ppFEV$_1$ of >12% within 2 weeks after Orkambi initiation

Discontinuation from Orkambi should primarily be due to a respiratory event. However, concomitant non-respiratory events will not exclude subjects from participation. Documentation of specific qualifying signs or symptoms is not required. Investigator attestation will be accepted if information is not present in source materials.

5. Resolution or stabilization of qualifying event(s) >28 days prior to Screening.

6. Discontinuation of Orkambi therapy must have occurred within approximately 12 weeks from the first dose of Orkambi. In the event that the subject reinitiated Orkambi, discontinuation of Orkambi therapy must have occurred within approximately 12 weeks from the time of the most recent initiation. Investigator attestation will be accepted if information is not present in source materials.

7. Homozygous for *F508del* as documented in the subject's medical record. If genotype documentation is not available in the medical record, genotyping will be performed during screening. If the screening genotype result is not received by the end of the Screening Period and all other eligibility criteria have been met, the subject may be randomized. *Note: Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study as described in Section 9.9.*

8. $FEV_1$ ≥25% and ≤90% of predicted normal for age, sex, and height (equations of Wang et al. or Hankinson et al. [12, 13]) at Screening Visit (Section 11.3.1). Spirometry measurements must meet American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria for acceptability and repeatability (Section 11.3.1).

9. Stable CF disease as judged by the investigator.

10. Willing to remain on a stable CF medication regimen from screening through the Safety Follow-up Contact.

## 8.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will **not** be eligible for this study:

1. History of any comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject

Examples of such comorbidities may include, but are not limited to:

- Respiratory:
  - Massive hemoptysis within the last 12 months
  - Any of the following within the past 12 months and not associated with an acute, resolved event:
    - Six-minute walk test distance <400 m
    - Resting arterial blood gas on room air showing $PaCO_2$ >50 mm Hg or $PaO_2$ <55 mm Hg
    - Systolic pulmonary arterial pressure (PAP) >35 mm Hg on echocardiography or a mean PAP >25 mm Hg measured by right heart catheterization, in the absence of a hypoxemic exacerbation or with an alternate etiology to explain the findings
- Non-respiratory: history of cirrhosis with portal hypertension, history of and/or risk factors for ventricular arrhythmia (e.g., long QT syndrome, hypokalemia, heart failure, left ventricular hypertrophy, bradycardia, myocardial infarction, cardiomyopathy, morbid obesity, acute neurologic events [subarachnoid hemorrhage, intracranial hemorrhage, cerebrovascular accident, and intracranial trauma], autonomic neuropathy, and significant anemia)

2. Recent rapid or progressive deterioration in respiratory status

3. Receiving continuous oxygen at >2 L/min or on face-mask ventilation

4. Any of the following abnormal laboratory values at Screening:

- Abnormal liver function defined as any 2 or more of the following: ≥3 × upper limit of normal (ULN) aspartate transferase (AST), ≥3 × ULN alanine transferase (ALT), ≥3 × ULN gamma-glutamyl transpeptidase, ≥3 × ULN alkaline phosphatase (ALP), or ≥2 × ULN total bilirubin.
- Abnormal liver function defined as any increase of ≥5 × ULN AST or ALT.
- Abnormal renal function defined as glomerular filtration rate ≤50 mL/min/1.73 $m^2$ (calculated by the Modification of Diet in Renal Disease Study Equation) for subjects ≥18 years of age and ≤45 mL/min/1.73 $m^2$ (calculated by the Counahan-Barratt equation) for subjects aged 12 to 17 years (inclusive).

5. Child-Pugh Class B or C hepatic impairment

6. An acute upper or lower respiratory infection, pulmonary exacerbation, or change in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug)

7. Documentation of colonization with organisms associated with a more rapid decline in pulmonary status (e.g. *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*)

8. History of lung transplantation since most recent initiation of Orkambi

9. History of alcohol or drug abuse in the past year as deemed by the investigator, including but not limited to cannabis, cocaine, and opiates

10. Participation in an investigational drug study or use of a CFTR modulator (including Orkambi) within 28 days or 5 terminal half-lives before screening of the previous investigational study drug or CFTR modulator, whichever is longer

- Ongoing participation in a noninterventional study (including observational studies and studies requiring assessments without administration of study drug) is permitted.

11. Use of restricted medications or foods within the specified window before the first dose of study drug, or an anticipated need or use of restricted medication or foods after the first dose of study drug, as defined in Table 9-1

12. Pregnant or nursing females: Females of child-bearing potential must have a negative pregnancy test at Screening and Day 1

13. The subject or a close relative of the subject is the investigator or a sub-investigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study. An adult (aged 18 years or older) who is a relative of a study staff member may be randomized in the study provided that

- the adult lives independently of and does not reside with the study staff member, or
- the adult participates in the study at a site other than the site at which the family member is employed.

# 9 STUDY IMPLEMENTATION

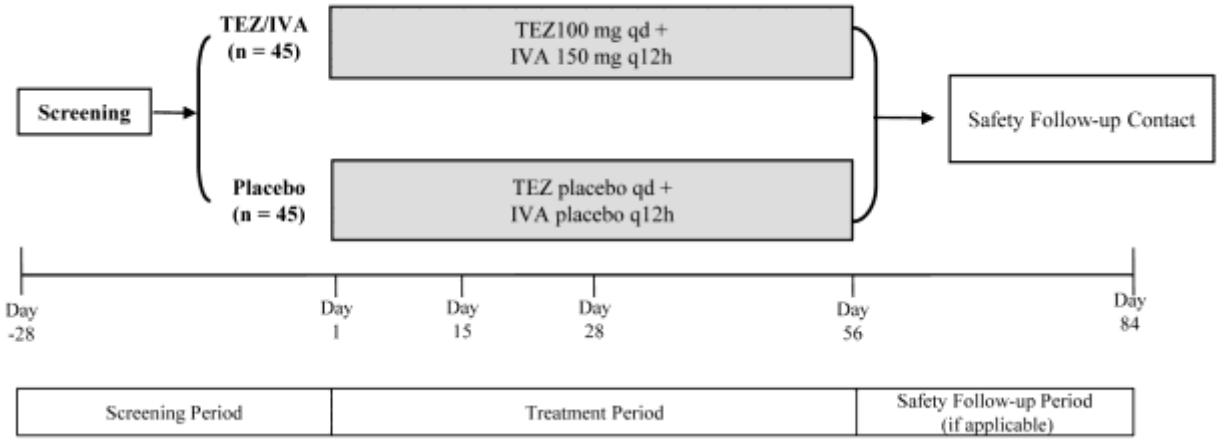
## 9.1 Study Design

Study VX16-661-114 (Study 114) is a Phase 3b, randomized, double-blind, placebo-controlled, parallel group, multicenter study in subjects aged 12 years and older with CF who are homozygous for *F508del* and who discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment. This study is designed to evaluate the safety and efficacy of TEZ/IVA.

This study includes a Screening Period (up to 28 days), Treatment Period (approximately 56 days), and Safety Follow-up Period (approximately 28 days). Approximately 90 subjects will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), sex (male versus female), and $ppFEV_1$ (determined during the Screening Visit; <40% versus ≥40% predicted) and then randomized 1:1 between the 2 study arms.

Subjects who complete the Day 56 Visit will be offered the opportunity to receive TEZ/IVA through the Expanded Access Program if they meet eligibility requirements for that program.

**Figure 9-1 Study VX16-661-114 Design**




Note: Clinical visits are on Days -28, 1, 15, 28, and 56. A telephone contact on Day 3 collects AEs. The Safety Follow-up may be a clinic visit or telephone call.

### 9.1.1 Screening

Screening Visit assessments are listed in Table 3-1.

Screening will occur within 28 days before administration of first dose of study drug. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent/assent from each subject.

#### 9.1.1.1 Repetition of Screening Assessment(s)

Repetition of individual screening assessment(s) that did not meet eligibility criteria is not permitted with the following exceptions:

- If there is clear evidence of a laboratory error (e.g., hemolyzed sample) or equipment malfunction, collection of a repeat sample for the appropriate laboratory test or assessment may be permitted with the approval of the medical monitor.

- Exclusionary liver function test (LFT) levels, which may be retested within 14 days of the original screening date

If screening spirometry measurements fail to meet acceptability or repeatability criteria as specified by ATS/ERS guidelines[6], repeat spirometry evaluation may be performed once.

If repeat values of the individual assessment(s) are within the eligibility criteria and completed within the screening window, then the subject is eligible for the study.

#### 9.1.1.2 Rescreening

Subjects may only be rescreened with the approval of the medical monitor. If a subject is rescreened, all screening assessments will be repeated except for *CFTR* genotyping, follicle-stimulating hormone (FSH) level (if serum FSH level was ≥40 mIU/mL during prior screening), and ophthalmologic examination. If a subject is rescreened, the screening window will begin after the first rescreening assessment has been initiated.

#### 9.1.1.3 Extension of Screening Period Window

A subject may have the Screening Period window extended by 4 weeks for the following reasons:

- Repetition of the Screening Period assessments (Section 9.1.1.1)
- Unexpected operational or logistic delays, or to meet the eligibility criteria
- Scheduling of ophthalmologic examination (Section 11.4.7)
- Repetition of spirometry assessment if results are of poor quality

### 9.1.2 Treatment Period

The Treatment Period will last approximately 56 days. Subjects will be randomized to 1 of 2 treatment arms: TEZ/IVA or placebo. The dosing regimen for each treatment arm is shown in Figure 9-1 and is as follows:

- TEZ/IVA: TEZ 100-mg/ IVA 150-mg fixed-dose combination (light yellow) film-coated tablet for oral administration (morning dose); IVA 150-mg (light blue) film-coated tablet for oral administration (evening dose)
- Placebo: 0 mg film-coated matching placebo tablets for oral administration (1 light yellow for the morning dose and 1 light blue for the evening dose)

The first dose of study drug will be administered after randomization on Day 1. Dosing details are given in Section 9.5.

Study visits during the Treatment Period will occur as shown in Table 3-2. Subjects will be outpatients during the Treatment Period unless hospitalized for illness. All visits should occur within the windows specified.

### 9.1.3 Safety Follow-up Contact

A Safety Follow-up Contact will be performed for the purpose of collecting information on AEs 28 days (±7 days) after the last dose of study drug. The assessments performed at the Safety Follow-up Contact are listed in Table 3-2. The Safety Follow-up Contact may be a telephone

interview; however, if deemed necessary by the investigator, a Safety Follow-up Visit may be required with necessary assessments to be determined by the investigator.

Subjects who prematurely discontinue treatment may not be required to have a Safety Follow-up Contact; refer to Section 9.1.4 for details.

### 9.1.4 Early Termination of Treatment

If a subject prematurely discontinues study treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. These subjects will also be required to complete a Safety Follow-up Contact 28 days (± 7 days) after their last dose of study drug.

If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Contact, and a separate Safety Follow-up Contact will not be required.

If a subject withdraws consent for the study, no further visits will be required (including an ETT or Safety Follow-up Contact), no further evaluations will be performed, and no additional data will be collected. Vertex may retain and continue to use any data collected before such withdrawal of consent.

### 9.1.5 Independent Data Monitoring Committee

An IDMC will be formed for this study. The safety and tolerability data will be reviewed by an IDMC to ensure the safety of the subjects in the study. Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be included in the IDMC charter. The IDMC charter will be finalized before the first subject is screened.

## 9.2 Rationale for Study Design and Study Drug Regimens

### 9.2.1 Study Design

A randomized, double-blind study design will avoid observer bias and reduce symptoms or outcomes arising from the subjects' knowledge of treatment.

Subjects will be randomized to receive TEZ in combination with IVA, or a matched placebo regimen. All subjects enrolled in the study will continue their normal, stable treatment for CF symptoms throughout the study.

Orkambi is the only therapy approved for subjects homozygous for the *F508del-CFTR* mutation that targets the underlying cause of CF. TEZ, an experimental CFTR corrector, in combination with IVA, is currently being evaluated in several Phase 3 studies in subjects who are both homozygous for *F508del* and heterozygous for *F508del* with other CFTR mutations. Scheduled IDMC reviews of each of the TEZ/IVA Phase 3 studies are completed and did not reveal any safety signals. Since subjects entering this study are not taking corrector/potentiator therapy, the use of placebo in this study is deemed ethical and necessary to adequately assess the benefit of treatment with TEZ in combination with IVA.

Study 114 is designed to compare active treatment with TEZ 100 mg daily (qd)/IVA 150 mg every 12 hours (q12h) with a matched placebo treatment for 8 weeks. The 8-week duration was selected to allow adequate exposure to TEZ/IVA to assess both the safety and efficacy of the treatment. This is appropriate because patients who have respiratory AEs with Orkambi typically do so within the first week of exposure, and a significant response in $ppFEV_1$ is expected after

14 to 28 days of treatment with TEZ/IVA. In addition, the 8-week duration was selected to allow a robust assessment of the durability of response that will be less affected by short-term variability in $ppFEV_{1,}$ and to facilitate the demonstration of significant changes in secondary endpoints, including CFQ-R.

### 9.2.2 Study Drug Dose

The dose regimen of TEZ chosen for continued development in Phase 3 was evaluated in Study 101, a Phase 2 study in 2 CF populations: one that was homozygous for *F508del* and one that was heterozygous for *F508del* and *G551D*. The dose regimen of TEZ 100 mg qd in combination with IVA 150 mg q12h provided clinically meaningful and statistically significant improvements in $ppFEV_1$ in both populations. Pivotal Phase 3 studies are ongoing; therefore, results are not known.

### 9.2.3 Rationale for Study Assessments

Safety assessments are standard parameters for clinical studies in drug development. The efficacy assessments are widely accepted and generally recognized as reliable, accurate, and relevant to the study of patients with CF.

Spirometry: Since lung disease is the major cause of morbidity and mortality for patients with CF, CF lung disease is the desired primary target of TEZ/IVA cotherapy. Spirometry is the most widely implemented standardized assessment to evaluate lung function. Predose and postdose spirometry assessments must be performed in all subjects according to the Schedule of Assessments (Table 3-1 and Table 3-2).

CFQ-R: The CFQ-R is a frequently used CF-specific instrument that measures the health-related quality of life of patients with CF.[7-9] As both IVA alone and TEZ/IVA are systemic therapies, they have the potential to improve not only respiratory symptoms but other extrapulmonary manifestations of CF as well. These improvements can be captured by the non-respiratory symptoms domains of the CFQ-R. The adolescent/adult version, the parent/caregiver version, and the child version measure quality-of-life domains, including respiratory symptoms, digestive symptoms, emotion, and health perception. Linguistically validated versions of the CFQ-R[10, 11] are available, thereby allowing consistent interpretation of the results in this global study. The CFQ-R will be used to capture and evaluate the impact of TEZ/IVA on patient reports of respiratory symptoms and other aspects of health-related quality of life.

## 9.3 Study Restrictions

Prohibited medications and certain foods are not allowed in this study (Screening Period through the Safety Follow-up Contact) (Table 9-1). Both TEZ and IVA are metabolized predominantly via the hepatic enzymatic pathway using CYP3A4. Therefore, the use of known moderate and strong inducers and inhibitors of CYP3A, which have the potential to significantly alter the exposure of TEZ and IVA, will be restricted in this study.

A non-exhaustive list of study prohibitions and cautions for food and medication will be provided in the Study Reference Manual.

**Table 9-1 Study Restrictions**

| | Study Period | |
|---|---|---|
| **Restricted Medication/Food** | **Screening Period** | **Treatment Period** |
| Certain fruits and fruit juices (Grapefruit, grapefruit juice, Seville oranges, marmalade) | None allowed within 14 days before the first dose of study drug | None allowed through the Safety Follow-up Contact |
| Moderate and strong CYP3A inducers | None allowed within 14 days before the first dose of study drug | None allowed through the Safety Follow-up Contact |
| Moderate and strong CYP3A inhibitors (except ciprofloxacin) | None allowed within 14 days before the first dose of study drug | None allowed through the Safety Follow-up Contact |
| Commercially available CFTR modulators (e.g., Kalydeco, Orkambi, or others) | None allowed within 28 days or 5 terminal half-lives before screening, whichever is longer | None allowed through the Safety Follow-up Contact |

CFTR: cystic fibrosis conductance regulator; CYP: cytochrome P450
Note: The use of restricted medication by subjects with medical needs will be addressed on a case-by-case basis with the medical monitor.

## 9.4 Prior and Concomitant Medications

Information regarding all prior and concomitant medications, including the subject's CF medications, other medications, and herbal and naturopathic remedies administered from 28 days before the Screening Visit through the Safety Follow-up Contact, if applicable, will be recorded in each subject's source documents. For subjects who are screened but are not subsequently randomized in the study, details of prior medication will only be documented in the subjects' source documents.

- Subjects must remain on a stable medication regimen for their CF from screening through the Safety Follow-up Contact; this includes supplements and inhaled antibiotics. A stable medication regimen is defined as the current medication regimen for CF that subjects have been following for at least 28 days before Day 1. Any potential exceptions to this must be discussed and approved by the Vertex medical monitor. Guidelines for a stable inhaled antibiotic regimen for CF are as follows:
    - Subjects who are taking daily inhaled tobramycin or other chronically inhaled antibiotics should remain on that drug at the current regimen throughout the study.
    - Subjects who are on inhaled cycling antibiotics should continue on their current schedule. The timing of the first dose of study drug should be synchronized as closely as possible to the first day of inhaled cycling antibiotics.
    - Subjects who alternate 2 different antibiotics monthly should remain on the same schedule during the study. The timing of the first dose of study drug should be synchronized as closely as possible to the first day of either of the inhaled antibiotics.
- There are no restrictions on the concomitant use of corticosteroids.
- Information about bronchodilator use during the study will be collected and documented. Subjects who are using a bronchodilator must have their spirometry assessments performed according to the guidelines provided in Section 11.3.1.

## 9.5 Administration

Study drug tablets will be administered orally. Subjects will swallow the study drug whole, and will not chew the drug before swallowing. Study drug tablets will be administered orally. Subjects will receive the same number of tablets each day to maintain the blind. Refer to Table 9-2.

**Table 9-2 Study Drug Administration - Treatment Period**

| Treatment Arm | Time | Drug(s) and Dose(s) Administered Route of Administration |
|---|---|---|
| **TEZ/IVA** | AM | TEZ 100-mg/IVA 150-mg fixed-dose tablet oral |
| | PM | IVA 150-mg tablet oral |
| **Placebo** | AM | TEZ/IVA-matching placebo tablet oral |
| | PM | IVA-matching placebo tablet oral |

AM: morning; IVA: ivacaftor; TEZ: tezacaftor; PM: evening.

Study drug administration guidelines:

1. Study drug should be administered within 30 minutes after starting a fat-containing meal, such as a standard CF high-fat, high-calorie meal or snack. It is recommended that study drug be administered after the start of and before the end of a meal, and that the duration of each meal associated with study drug intake (i.e., breakfast and dinner/snack, as applicable) should not exceed 30 minutes.
2. On days with no scheduled clinic visits, study drug should be administered q12h (± 2 hours). For each subject, all doses (morning [TEZ/IVA] and evening [IVA], or matching placebo) of study drugs will be taken at approximately the same time each day. For example, if the morning dose is taken at 08:00 every morning, the evening dose should be taken at 20:00 every evening (but it could be taken between 18:00 and 22:00).
3. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. The meal or snack will be provided by the site for the morning dose of study drug.
4. If a subject's scheduled visit is to occur in the afternoon, the following guidelines must be used:
    - If the dose in the clinic will be within 6 hours of the subject's scheduled morning dose, the subject should withhold their morning dose of study drug and the morning dose will be administered in the clinic.
    - If the dose in the clinic will be more than 6 hours after the subject's scheduled morning dose, the subject should take the morning dose at home and the evening dose will be administered in the clinic. In this event, all assessments will be collected relative to the evening dose.
5. For visits after the Day 1 Visit, subjects will be instructed to bring all used and unused materials associated with study drug to the site; study drug will be dispensed at each visit, as appropriate.

## 9.6 Dose Modification for Toxicity

Dosages of TEZ or IVA cannot be changed, but the investigator can interrupt or stop treatment.

## 9.7 Study Drug interruption

If study drug dosing must be interrupted for more than 72 hours, the medical monitor must be notified. In these instances, study drug dosing may only resume after approval by the medical monitor. Specific instructions for interruption due to elevated LFT levels are provided in Section 11.4.6.

It is recommended that study drug should not be interrupted during a pulmonary exacerbation unless, in the opinion of the investigator, it would be in the best interest of the subject.

## 9.8 Missed Doses

If a subject misses a dose and recalls the missed dose within 6 hours, the subject should take his/her dose with food. If more than 6 hours have elapsed after his/her usual dosing time, the subject should skip that dose and resume his/her normal schedule for the following dose. For example,

- if the morning dose of study drug should have been taken at approximately 08:00, and the subject remembers at 12:00 that he/she forgot to take his/her dose, he/she should take the dose with food as soon as possible.
- if the morning dose of study drug should have been taken at approximately 08:00, and more than 6 hours have elapsed beyond the scheduled dosing time (i.e., the time is past 14:00), the subject would resume dosing with the evening dose at approximately 20:00.

## 9.9 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. If a subject has been withdrawn from study drug treatment, the subject should continue to be followed, provided the subject has not withdrawn consent.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document the subject's outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for an ETT and/or Safety Follow-up Contact, if applicable (Section 9.1.3, Section 9.1.4), and follow up with the subject regarding any unresolved AEs.

If the subject withdraws consent, no further visits will be required (including an ETT or Safety Follow-up Contact), no further evaluations will be performed, and no additional data will be collected. Vertex may retain and continue to use any data collected before such withdrawal of consent.

The investigator should inquire about the reason for withdrawal of consent.

Subjects must return all unused study drug.

A subject will be withdrawn from study drug treatment for any of the following reasons:

- A female subject or a female partner of a male subject has a confirmed pregnancy.
- Treatment unblinding by the investigator.
- Development of a life-threatening AE or a serious AE (SAE) that places him/her at immediate risk, and discontinuation of study drug treatment and withdrawal from the study are deemed necessary.
- Following randomization, the screening *CFTR* genotype results does not confirm study eligibility. The subject will undergo ETT and/or Safety Follow-up Contact per Section 9.1.3 and Section 9.1.4, and will then be discontinued from the study. After discontinuation of study drug treatment, the subject will not undergo any further assessments other than those performed at the ETT and/or Safety Follow-up Contact.

A subject may be withdrawn from study drug treatment after a discussion between the investigator and the medical monitor for any of the following reasons:

- Development of a medical condition that requires prolonged concomitant therapy with a prohibited medication or prolonged interruption of the study drug.
- Noncompliance with study requirements.
- An increase in liver function studies according to evaluations and management described in Section 11.4.6.
- Development of a cataract or lens opacity.

### 9.10 Replacement of Subjects

Subjects who withdraw or are withdrawn during the study drug treatment period(s) will not be replaced.

## 10 STUDY DRUG INFORMATION AND MANAGEMENT

### 10.1 Preparation and Dispensing

Study drug may be dispensed only under the supervision of the investigator or an authorized designee and only for administration to the study subjects.

### 10.2 Method of Assigning Subjects to Treatment Groups

An interactive web response system (IWRS) will be used to assign subjects to treatment. Randomization may occur on Day -1. Detailed instructions for randomization will be provided separately.

## 10.3 Packaging and Labeling

Study drug tablets will be supplied in blister cards by Vertex. Study drug cards will be provided and replaced via the IWRS. A detailed study drug dispensation plan will be provided in the Pharmacy Manual.

Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for TEZ/IVA and IVA will be included in the Pharmacy Manual.

## 10.4 Study Drug Supply, Storage, and Handling

TEZ 100 mg/IVA 150 mg and matching placebo will be supplied as light yellow film-coated tablets of similar size and appearance containing TEZ 100 mg/IVA 150 mg and TEZ 0 mg/IVA0 mg, respectively.

IVA (150 mg) and matching placebo will be supplied as light blue film-coated tablets of similar size and appearance containing IVA 150 mg and IVA 0 mg, respectively.

Blister cards must be stored at room temperature according to Table 10-1 and to the instructions provided in the Pharmacy Manual. While at the clinical site, the study drug must be stored in a secure, temperature-monitored area of limited access and only at the location(s) listed on the Form FDA 1572 (or Investigator Statement). While at the clinical site, the investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational products are stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for per instructions in Section 10.5.

Instructions regarding the storage and handling of study drug after dispensation to subjects will be provided to sites in the Pharmacy Manual.

**Table 10-1 Identity of Study Drugs, Dosage, and Storage**

| Drug Name | Strength/Formulation/Route | Dosage | Storage Condition |
|---|---|---|---|
| TEZ/IVA fixed-dose tablet | 100-mg/150-mg tablet; oral | 100 mg/150 mg, morning dose | ≤25°C (77°F) with excursions to 30°C (86°F) |
| IVA | 150-mg tablet, oral | 150 mg, evening dose | ≤25°C (77°F) with excursions to 30°C (86°F) |
| TEZ/IVA-matching placebo | 0-mg/0-mg tablet; oral | 0 mg/0 mg, morning dose | ≤25°C (77°F) with excursions to 30°C (86°F) |
| IVA-matching placebo | 0-mg tablet, oral | 0 mg, evening dose | ≤25°C (77°F) with excursions to 30°C (86°F) |

## 10.5 Drug Accountability

The pharmacist or designated site staff will maintain records documenting the dates and amounts of study drug received, study drug dispensed to the subjects, and study drug returned by the subjects.

Subjects will be instructed to return all used, partially used, and full study drug blister cards to the site. These materials will be retained at the site according to instructions provided by Vertex or its designee until inventoried by the study monitor. The study monitor will review study drug records and inventory throughout the study.

## 10.6 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subjects until the study monitor has performed drug accountability. At the end of the study, the study monitor will provide instructions as to the disposition of any unused investigational product. If the study monitor authorizes destruction at the study site, the investigator will ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Vertex. Destruction will be adequately documented.

Procedures for destruction or return of the study drug will be detailed in the Pharmacy Manual.

## 10.7 Compliance

To maximize treatment compliance, the investigator or designee will supervise all study drug dosing that occurs at the site. At each visit, site personnel will review subject compliance with study drug dosing and remind the subject of study drug dosing requirements. Compliance will also be assessed by ongoing study drug count.

If a subject demonstrates continued noncompliance of study drug dosing despite educational efforts, the investigator should contact the medical monitor to discuss potential discontinuation of the subject from the study treatment.

## 10.8 Blinding and Unblinding

This is a double-blind study.

### 10.8.1 Blinding

All study personnel will be blinded to subject treatment assignments except for the following individuals:

- 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 the fetus in the event of a pregnancy
- The unblinded site monitor and unblinded trip report reviewer
- An unblinded pharmacist at the contract research organization (CRO) for dispensing study drug
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations
- External vendor (unblinded) statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IXRS Management for IWRS oversight and system administration
- Vertex Clinical Supply Chain

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

**Spirometry Data Blinding**

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

### 10.8.2 Unblinding

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

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

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

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

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor will be notified within 24 hours of the unblinding event. The reason and the date of the unblinding will be documented clearly in the subject's study file. Information about the treatment assignment obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with the sponsor (Vertex), CRO, or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered a serious adverse event (SAE), according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex Global Patient Safety (GPS) or designee, per Section 13.1.2.

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.

# 11 ASSESSMENTS

## 11.1 Timing of Assessments

The timing of assessments is shown in Table 3-1 and Table 3-2.

### 11.1.1 Informed Consent/Assent

Each subject of age of consent (per local requirements) must sign and date a study-specific ICF before any study-specific procedures can be performed. Subjects not of age of consent must assent, if applicable per local requirements, to participate in the study, and the subject's parent or legal guardian must sign and date a study-specific ICF before any study-specific procedures can be performed. The consent forms will comply with all applicable regulations governing the protection of human subjects. An ICF and Assent Form, approved by Vertex and the site's institutional review board (IRB) or independent ethics committee (IEC), must be used.

### 11.1.2 Assigning Subject Number

After a subject has signed an ICF or Assent Form, if applicable, a subject number will be assigned. The subject will retain this number for the entire study. Detailed instructions on assigning subject numbers will be provided in the Study Reference Manual. If a subject is rescreened, the subject retains the original subject number.

## 11.2 Subject and Disease Characteristics

Subject and disease characteristics include demographics, medical history, height, and weight.

Medical history will be collected from each subject during screening. The medical history shall include a complete review of systems, past medical and surgical histories, and any allergies. Based on the medical history, the subject will be assessed for any disqualifying medical conditions as specified in the inclusion and exclusion criteria.

## 11.3 Efficacy

### 11.3.1 Spirometry

Spirometry will be performed according to the ATS/ERS guidelines[6] at the time points noted in Table 3-1 and Table 3-2 according to the additional guidelines that follow.

Prebronchodilator spirometry is defined as spirometry testing performed for subjects who have

- withheld their short-acting bronchodilators (e.g., albuterol) or anticholinergic (e.g., ipratropium bromide [Atrovent®]) for more than 4 hours before the spirometry assessment
- withheld their twice-daily, long-acting bronchodilator (e.g., salmeterol) for more than 12 hours before the spirometry assessment; and
- withheld their once-daily, long-acting bronchodilator (e.g., tiotropium bromide [Spiriva®]) for more than 24 hours before the spirometry assessment

During the Treatment Period, all spirometry assessments must be performed before dosing, except on Day 1, when in addition to the predose assessments, 2 postdose spirometry assessments will be performed 2 hours (±30 minutes) and 4 hours (±30 minutes) after dosing. If the Day 1 predose spirometry is performed postbronchodilator, the subject should withhold any

further bronchodilator use until completion of the 4-hour postdose spirometry assessment on that day.

During the Screening Period, spirometry assessments may be performed pre- or post-bronchodilator. At all the other visits, all spirometry assessments should be performed prebronchodilator.

In the event that a subject forgets to withhold bronchodilator(s), spirometry should be performed according to the following:

- If a subject's Day 1 spirometry is performed prebronchodilator, but on a subsequent visit the subject does not withhold bronchodilator, a postbronchodilator spirometry will be obtained for that visit only, and the visit will not be rescheduled.
- If a subject does not withhold his/her dose of bronchodilator on Day 1, spirometry at that visit and at all subsequent visits (according to the schedule of assessments detailed in Table 3-2) should be performed postbronchodilator.
- Each spirometry assessment will be recorded in the source documents as pre- or post-bronchodilator.

All sites will be provided with spirometers to be used for all study assessments. Spirometry data will be transmitted to a centralized spirometry service for quality review.

Subjects and their parent/caregiver should not be informed of their study-related spirometry results from Day 1 through Day 56, regardless of whether the subject prematurely discontinues treatment.

The parameters listed below will be normalized using the standards of Wang et al (for female subjects aged 12 to 15 years [inclusive] and male subjects aged 12 to 17 years [inclusive]) or Hankinson et al (for female subjects aged 16 years and older and male subjects aged 18 years and older)[12, 13]:

- $FEV_1$ (L)
- Forced vital capacity (FVC) (L)
- $FEV_1$/FVC (ratio)
- Forced expiratory flow 25% to 75% (L/s)

Subjects in whom the Wang standard is applied at the Screening Visit will have the Wang standard applied throughout the study, even if there is a change in age during the course of the study that would otherwise necessitate use of the Hankinson standard.

### 11.3.2 Cystic Fibrosis Questionnaire-Revised

Subjects will be asked to complete the CFQ-R in their native language.[14] The CFQ-R will be completed before the start of any other assessments, as noted in Table 3-2. Subjects who are <14 years of age at Day 1 will complete the CFQ-R child version themselves, and their parents/caregivers will complete the CFQ-R Parent version, at all visits, regardless of whether the subject subsequently turns 14 years of age during the study. Subjects 14 years of age and older at Day 1 will complete the adolescent/adult version of the questionnaire themselves at all visits. The questionnaires provide information about demographics; general quality of life, school, work, or daily activities; and symptom difficulties (pertaining to CF). Copies of the

CFQ-R used in this study will be provided in the Study Reference Manual. Validated translations of the CFQ-R, if available, will be provided for participating centers in non-English-speaking countries.

## 11.4 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, pulse oximetry, postdose spirometry, and physical examinations (PEs).

### 11.4.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with ICH GCP guidelines. Section 13.1 outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting AEs. A separate document that details AE case report form (CRF) completion guidelines for investigators as well as training will be provided.

### 11.4.2 Clinical Laboratory Assessments

Blood samples will be collected before dosing and analyzed at a central laboratory unless otherwise specified. A local laboratory may be used if a subject cannot return to the clinical study site for mandatory liver function testing (Section 11.4.6).

Blood samples for clinical laboratory assessments will be collected according to the schedule shown in Table 3-1 and Table 3-2. Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1.1.2).

The safety laboratory test panels are shown in Table 11-1.

**Table 11-1 Safety Laboratory Test Panels**

| Serum Chemistry | Hematology | Urinalysis[a] |
|---|---|---|
| Glucose | Hemoglobin | Leukocyte esterase |
| Blood urea nitrogen | Erythrocytes | Nitrite |
| Creatinine | Mean corpuscular hemoglobin | Urobilinogen |
| Sodium | Mean corpuscular hemoglobin concentration | Urine protein |
| Potassium | Mean corpuscular volume | pH |
| Calcium | Reticulocytes | Urine blood |
| Chloride | Platelets | Specific gravity |
| Magnesium | Leukocytes | Urine ketones |
| Bicarbonate | Differential (absolute and percent): | Urine bilirubin |
| Inorganic phosphate | Eosinophils | Urine glucose |
| Total bilirubin, direct bilirubin | Basophils | Urine potassium |
| Alkaline phosphatase | Neutrophils | Urine sodium |
| Aspartate aminotransferase | Lymphocytes | |
| Alanine aminotransferase | Monocytes | |
| Lactate dehydrogenase | **Coagulation Studies** | |
| Gamma-glutamyl transpeptidase | Activated partial thromboplastin time | |
| Total protein | Prothrombin time | |
| Albumin | Prothrombin time International Normalized Ratio | |
| Creatine kinase | | |
| Amylase | | |
| Lipase | | |

[a] If urine is positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be performed for leukocytes, erythrocytes, crystals, bacteria, and casts.

Pregnancy (β-human chorionic gonadotropin) Tests for Females of Childbearing Potential: Serum samples will be obtained as specified in Table 3-1 and Table 3-2 and analyzed at the central laboratory. Urine pregnancy tests will be performed at the site as specified in Table 3-2. The urine pregnancy test on Day 1 must be negative before the first dose of study drug.

FSH (Screening Period only): Blood sample for FSH will be measured for any potentially postmenopausal female. In addition to at least 12 months of continuous spontaneous amenorrhea, serum FSH levels must be ≥40 mIU/mL for the subject to be considered postmenopausal.

*CFTR* Genotype (Screening Period only): *CFTR* genotyping will be performed at the Screening Visit only if the *CFTR* genotype is not documented in the subject's medical record.

Additional evaluations: Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate.

For purposes of study conduct, only laboratory tests done in the central laboratory may be used. At the discretion of the local investigator, local laboratories may be used for management of urgent medical issues. If a local laboratory test value is found to be abnormal and clinically

significant, it should be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. If it is not possible to send a timely specimen to the central laboratory (e.g., the subject was hospitalized elsewhere), the investigator may base the assessment of an AE on the local laboratory value.

### 11.4.3 Physical Examinations and Vital Signs

A PE of all body systems and vital signs assessment will be performed at screening and select study visits (see Table 3-1and Table 3-2). At other visits, symptom-directed PEs and symptom-directed vital sign assessments can be performed at the discretion of the investigator or healthcare provider.

A PE includes a review of the following systems: head/neck/thyroid; eyes/ears/nose/throat; respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in PEs will be reported as AEs. Vital signs include blood pressure (systolic and diastolic), pulse rate, and respiration rate. These will be collected predose at all visits and will be assessed following at least a 5-minute rest in the seated or supine position.

### 11.4.4 Contraception and Pregnancy

The effects of TEZ/IVA on conception, pregnancy, and lactation in humans are not known.

#### 11.4.4.1 Contraception

Participation in this study requires a commitment from the subject and his/her partner to use at least 1 acceptable method of contraception, which must be used correctly with every act of sexual intercourse. Methods of contraception should be in successful use from at least 14 days before the first dose of study drug (unless otherwise noted) and until 90 days following the last dose of study drug.

**Contraception for the couple is waived for the following:**

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
- If the male is infertile (e.g., bilateral orchiectomy). Infertility may be documented through examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound before the first dose of the study drug.
- If the female is of non-childbearing potential, per the following:
  - Documented hysterectomy or a bilateral oophorectomy/salpingo-oophorectomy.
  - Postmenopausal: continuous amenorrhea for at least 12 months and serum FSH levels ≥40 mIU/mL.
  - Has not achieved menarche (has not had her first menstrual period). If a female achieves menarche during the study, she will need to follow acceptable methods of contraception or abstinence.

For subjects for whom contraception methods are not waived due to 1 of the reasons cited above, the following are acceptable contraceptive methods for male subjects and their female (non-study) partners, and for female subjects and their male (non-study) partners:

**Table 11-2 Acceptable Methods of Contraception**

- Male vasectomy 6 months or more previously, with a negative post-vasectomy semen analysis for sperm.
- Male or female condom with or without spermicide (either as a single product if commercially available and/or allowed according to local regulations; otherwise condom and spermicide as separate products).
- Female bilateral tubal ligation performed at least 6 months previously.
- Female diaphragm, cervical cap, or vaginal sponge, each with spermicide (where available).
- Female continuous use of an intrauterine device (non-hormone releasing or hormone releasing) for at least 90 days.
- Female combined (estrogen and progestogen-containing) or progestogen-only hormonal contraception associated with inhibition of ovulation if successfully used for at least 60 days.

**Important notes:**

- Local requirements may prohibit the use of some of these acceptable methods listed above. Please contact the medical monitor with any questions.
- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.
- Male and female subjects who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active.
- Female condom used with male condom (as a double method of contraception) is not an acceptable method of contraception due to risk of tearing; a different acceptable method of birth control must be used as described in Table 11-2.
- Male subjects must not donate sperm after the first dose of study drug, throughout the study, and for 90 days following the last dose of study drug.
- Female subjects and female partners of male subjects should not plan to become pregnant during the study through 90 days following the last dose of study drug.
- Female subjects should not nurse a child from the start of study drug dosing through 90 days following the last dose of study drug.

Unique situations that may not fall within the above specifications may be discussed with the Vertex medical monitor on an individual basis.

#### 11.4.4.2 Pregnancy

Subjects will be counseled to inform the investigator of any pregnancy that occurs during study treatment and for 90 days after the last dose of study drug(s).

All pregnancies occurring during the study or within 90 days after discontinuation of study drug must be followed until resolution (i.e., birth or voluntary or spontaneous termination of the pregnancy). Any subject found to be pregnant at any time during the study will be withdrawn from the study immediately. Any pregnancy outcome that meets the criteria for an SAE will be reported as an SAE.

If a subject or the female partner of a male subject becomes pregnant while participating in the study, study drug will be permanently discontinued immediately. The investigator will notify Vertex GPS within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form.

The subject or partner will be followed until the end of the pregnancy and the infant will be followed for 1 year after the birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

### 11.4.5 Pulse Oximetry

Pulse oximetry is a noninvasive measure of oxygen delivery to the tissues and has been correlated with clinical status and lung function. Arterial oxygen saturation by pulse oximetry will be measured at visits noted in Table 3-1 and Table 3-2 and will be assessed following at least a 5-minute rest (seated or supine). Pulse oximetry will be collected before study drug dosing at all visits.

### 11.4.6 Liver Function Test Parameters

Liver Function Testing

Liver function testing must be performed as noted in Table 3-2 while subjects are receiving study drug treatment and at the ETT visit when indicated. These blood samples should be processed and shipped immediately per the Laboratory Manual.

Subjects with new treatment-emergent ALT or AST elevations of >3 × ULN and clinical symptoms must be followed closely, including repeat confirmatory testing performed by the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT and AST levels, as clinically indicated. In addition, if ALT or AST is >5 × ULN, repeat follow-up levels must be obtained within 7 ± 2 days.

If a subject cannot return to the site for liver function testing, a local laboratory may be used. Elevations in LFTs at the local laboratory must be reported immediately to the medical monitor, and the subject must have the tests repeated and sent to the central laboratory as soon as possible (ideally within 48 to 72 hours).

Study Drug Interruption

Study drug administration **must be interrupted** immediately (prior to confirmatory testing), and the medical monitor must be notified, if any of the following criteria is met and confirmed with repeat testing:

- ALT or AST >8 × ULN
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN in association with total bilirubin >2 × ULN and/or clinical jaundice

A thorough investigation of potential causes should be conducted, and the subject should be followed closely for clinical progression.

If no convincing alternative etiology (e.g., acetaminophen use, viral hepatitis, or alcohol ingestion) for the elevated tests is identified, regardless of whether the levels have improved, study drug treatment must be permanently discontinued if repeat testing within 48 to 72 hours confirms the initial elevation. Subjects in whom treatment is discontinued for elevated liver tests should have them monitored closely until levels normalize or return to baseline.

Resumption of Study Drug
If an alternative, reversible cause of liver test elevation(s) has been identified, study drug may be resumed once the levels return to baseline or are ≤2 × ULN, whichever is higher. Approval of the medical monitor is required before resumption of study drug. Upon resumption of study drug, levels should be assessed weekly for 4 weeks. If a protocol-defined elevation occurs within 4 weeks of rechallenge with study drug (with confirmation of the initial elevation by repeat testing within 48 to 72 hours), then the study drug treatment must be permanently discontinued, regardless of the presumed etiology.

### 11.4.7 Ophthalmologic Examination

Subjects <18 years of age who did not have an ophthalmological examination prior to starting Orkambi will undergo an ophthalmologic examination if they have not had an ophthalmologic examination within 6 months before the Screening Period. The examination must be performed by a licensed ophthalmologist or optometrist at screening and includes

- measurement of best corrected distance visual acuity of each eye
- pharmacologically dilated examination of the lens with a slit lamp

The screening ophthalmologic examination must be completed before randomization. Subjects who have documentation of bilateral lens removal do not need the ophthalmologic examination.

Additional ophthalmologic examinations may be conducted at the discretion of the investigator. The medical monitor should be notified of any abnormal findings from additional ophthalmologic examinations.

### 11.4.8 Spirometry

Postdose spirometry assessment will be performed 2 hours (± 30 minutes) and 4 hours (± 30 minutes) after dosing on Day 1; these assessments will be performed in addition to the predose spirometry assessment. If the Day 1 predose spirometry is performed postbronchodilator, the subject should withhold any further bronchodilator use until completion of the 4-hour postdose spirometry assessment on that day.

## 12 STATISTICAL AND ANALYTICAL PLANS

This section presents a summary of the planned analyses for this protocol. Statistical analysis details will be provided in the statistical analysis plan (SAP) which will be finalized before the clinical data lock for the study and treatment unblinding.

### 12.1 Sample Size Consideration

Sample size calculation is based on the key secondary endpoint of absolute change in $ppFEV_1$ to the average of the Day 28 and Day 56 measurements.

A Bayesian approach will be used to assess the treatment effect on the change in $ppFEV_1$. The study will be considered successful if the posterior probability that the treatment difference between TEZ/IVA and placebo is greater than 0 is at least 80%, using a noninformative prior distribution. Assuming a 3.0 percentage points mean treatment difference between TEZ/IVA and placebo and a standard deviation (SD) of 6.0 percentage points, with 42 TEZ/IVA subjects and 42 placebo subjects, the Bayesian power to achieve the posterior probability criterion is at least

90% (92.6%). After adjusting for an assumed dropout rate of 5% a total sample size of 90 subjects is needed.

[redacted]

## 12.2 Analysis Sets

Assignment of subjects to analysis sets will be done before the clinical data lock for the study.

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

The Full Analysis Set (FAS) is defined as all randomized subjects who have received at least 1 dose of study drug. The FAS will be used in efficacy analyses in which subjects will be analyzed according to their randomized treatment group.

The Safety Set is defined as all subjects who received at least 1 dose of study drug. The Safety Set is to be used for all safety and tolerability analyses, in which subjects will be analyzed according to the treatment they received.

## 12.3 Statistical Analysis

The primary objective of this study is to evaluate the respiratory safety of TEZ/IVA through Day 56 in subjects with CF homozygous for *F508del* and who discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment.

This section presents a summary of the planned statistical analyses of safety, efficacy, and tolerability. The Vertex Biometrics department or a designated CRO will analyze the data derived from this study. SAS® Version 9.2 or higher will be used to generate all statistical outputs (tables, figures, listings, and data sets).

Statistical analysis and presentation details will be provided in the SAP for the study.

### 12.3.1 General Considerations

All individual subject data for all randomized subjects exposed to 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, median, minimum value, and maximum value. The precision of the measurement for each continuous variable will be specified in the SAP.

**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 initial administration of study drug.

**Change (absolute change) from baseline** will be calculated as post-baseline value - baseline value.

**Relative change from baseline** will be calculated as (post-baseline value - baseline value)/baseline value.

The treatment-emergent (TE) period will include the time from the first dose to the Safety Follow-up Contact or 28 days after the last dose of the study drug for subjects who do not have a Safety Follow-up Contact.

### 12.3.2 Background Characteristics

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, study drug exposure and compliance, and other background characteristics will be summarized. Additionally, all subject data will be presented in subject data listings. All summaries will be based on the FAS unless otherwise specified in the SAP for the study. No statistical hypothesis testing will be performed.

#### 12.3.2.1 Subject Disposition

The number and percentage of subjects in the following categories will be summarized as appropriate:

- All Subjects Set
- Randomized
- Dosed (Safety Set)
- Randomized, dosed, and carry the intended *CFTR* mutation (see SAP Appendix 1) (FAS)
- Completed study drug treatment
- Prematurely discontinued the study during the Treatment Period and the reasons for discontinuation
- Completed study/Safety Follow-up Contact
- Prematurely discontinued the study and the reasons for discontinuation

#### 12.3.2.2 Demographics, Medical History, and Baseline Characteristics

Demographics, medical history, and baseline characteristics will be summarized.

The following demographics and baseline characteristics will be summarized by dose group for the FAS: sex, race, ethnicity, age, weight, height, region, baseline $ppFEV_1$, and baseline score of CFQ-R respiratory domain.

#### 12.3.2.3 Prior and Concomitant Medications

Medications used in this study will be coded by using the World Health Organization-Drug Dictionary Enhanced and categorized as the following:

- **Prior medication:** any medication that started before initial dosing of study drug, regardless of when it ended
- **Concomitant medication:** medication continued or newly received at or after initial dosing of study drug through the end of the TE Period
- **Post-treatment medication:** medication continued or newly received beyond the TE Period

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

Prior medications and concomitant medications will be summarized descriptively based on the FAS. Post-treatment medications will be listed for each subject.

#### 12.3.2.4 Study Drug Exposure and Compliance

Exposure to study drug (i.e., duration of treatment) will be summarized for the FAS in terms of duration of treatment a subject received (in days), defined as the last day minus the first day of study drug plus 1.

Dosing compliance will be summarized for the FAS and is calculated as the actual number of dosing occasions at which study drug was taken (including when administered at study visits), as a percentage of the planned number of dosing occasions.

Duration of treatment and dosing compliance will be summarized by means of descriptive summary statistics.

### 12.3.3 Safety Analysis

Respiratory safety of TEZ/IVA is the primary objective of this study and will be assessed in terms of AE incidence, including but not limited to the following:

- Chest discomfort
- Dyspnea (shortness of breath)
- Respiration abnormal (chest tightness)
- Asthma
- Bronchial hyperreactivity
- Bronchospasm
- Wheezing

All safety analyses will be based on the TE Period for subjects in the Safety Set.

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

- Incidence of treatment-emergent AEs, SAEs, and discontinuations due to AEs
- Clinical laboratory values
- Vital signs
- Pulse oximetry

All safety data will also be presented in individual subject data listings.

#### 12.3.3.1 Adverse Events

AEs will be coded according to MedDRA. The number and percentage of subjects experiencing an AE will be summarized by the MedDRA system organ class and preferred term, as well as by dose group. 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 AEs** are defined as AEs that were reported or worsened on or after the start of study drug dosing through the Safety Follow-up Contact.

Only TEAEs will be summarized in tables. All summaries of TEAEs will be presented by the severity of the AE and relationship to the study drug. Some rules that will apply to the summarization of AEs are (1) a subject with multiple occurrences of the same AE or a continuing AE will only be counted once; (2) only the maximum severity level will be presented in the severity summary; and (3) only the worst relationship level will be presented in the relationship summary.

AEs leading to death, SAEs, dose interruption, and permanent discontinuation will be listed separately. All AEs through the Safety Follow-up Contact will be listed in an individual subject data listing, including pretreatment AEs.

#### 12.3.3.2 Clinical Laboratory Assessments

For the laboratory measurements, the raw values and change from baseline values of the continuous hematology, coagulation, and chemistry results will be summarized in SI units at each scheduled time point.

The number and percentage of subjects with at least 1 assessment meeting threshold criteria during the Treatment Period will be summarized. The threshold criteria will be provided in the SAP.

A listing containing individual subject hematology, coagulation, and chemistry values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points. Results of urinalysis and pregnancy tests will be provided in data listings only.

#### 12.3.3.3 Vital Signs

For the on-treatment vital signs measurements, the raw values and change from baseline values will be summarized by treatment group at each scheduled time point during the TE Period: systolic and diastolic blood pressure (mm Hg), HR (beats per minute), and respiratory rate (breaths per minute).

Additional vital sign analyses will be described in the SAP, if applicable.

#### 12.3.3.4 Physical Examination

Physical examination findings will be presented as a data listing only.

#### 12.3.3.5 Pulse Oximetry

For the treatment-emergent pulse oximetry measurements, a summary of raw values and change from baseline values will be provided by treatment groups at each scheduled time point during the TE Period for the percent of oxygen saturation by pulse oximetry. In addition, the mean value at each visit will be plotted by treatment groups for the percent of oxygen saturation.

#### 12.3.3.6 Postdose Spirometry

For the 2-hour and 4-hour postdose measurements on Day 1, a summary of raw values for percent predicted $FEV_1$ will be provided by treatment at each time point. The absolute change from the Day 1 predose value of percent predicted $FEV_1$ will be summarized by treatment at each time point. In addition, the number and percentage of subjects with percent predicted $FEV_1$ decline of ≥10, ≥15, and ≥20 percentage points in the absolute change from the Day 1 predose value, and the number and percentage of subjects with percent predicted $FEV_1$ decline of ≥10, ≥15, and ≥20% in the relative change from Day 1 will be summarized by treatment and by assessment time.

### 12.3.4 Efficacy Analysis

#### 12.3.4.1 Analysis of Key Efficacy Variables

The actual posterior/conditional probability will be calculated for the probability of a greater than zero (>0) treatment effect difference in mean $ppFEV_1$ change between TEZ/IVA and placebo is greater than or equal to 80%, based on the observed data of the efficacy endpoint on the absolute change from baseline in $ppFEV_1$ to the average of the Day 28 and Day 56 measurements. This will serve as the primary efficacy analysis outcome.

Additionally, the key efficacy endpoint of the absolute change from baseline in ppFEV1 to the average of the Day 28 and Day 56 measurements will be analyzed using a mixed-effects model for repeated measures (MMRM) with $ppFEV_1$ at each time point as the outcome variable. The MMRM model will include the absolute change from baseline in $ppFEV_1$ at each visit as the dependent variable; treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect, with adjustment for sex (male versus female), age group at the Screening Visit (<18 versus ≥18 years old), and $ppFEV_1$ severity determined during the Screening (or baseline) Period (<40% versus ≥40% predicted).

The estimated treatment effect within TEZ/IVA and placebo arm, as well as the estimated treatment difference between TEZ/IVA and placebo arm will be provided based on the MMRM model along with 95% CI. These results will serve as additional efficacy outcomes, which is in addition to the primary actual posterior/conditional probability outcome. Furthermore, treatment effect and treatment difference at each post-baseline visit, obtained from the model, will also be provided.

[redacted]

#### 12.3.4.2 Analysis of Secondary Efficacy Variables

- **Relative change in ppFEV$_1$ from baseline to the average of the Day 28 and Day 56 measurements:** Analysis of this variable will be similar to the key efficacy analysis using an MMRM model but without calculation of the posterior/conditional probability based on this variable.
- **Absolute change in the CFQ-R respiratory domain score from baseline to the average of the Day 28 and Day 56 measurements:** Analysis of this domain will be similar to the key efficacy using an MMRM model but without calculation of the posterior/conditional probability based on this variable, with the addition of the CFQ-R respiratory domain score at baseline as a covariate.

[redacted]

### 12.3.5 Tolerability Analysis

A tolerability analysis will be based on the Safety Set for a standard summary of study drug discontinuation rate. Rate will be reported as descriptive statistics in counts and percentages, separately by the TEZ/IVA arm and the placebo arm. No statistical hypothesis testing will be performed. An additional summary of the tolerability outcome including but not limited to study/study drug discontinuation rate by reasons, by AE of special interest, and by time to discontinuation will also be reported.

[redacted]

#### 12.3.5.2 IDMC Analysis

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

# 13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

## 13.1 Adverse Event and Serious Adverse Event Documentation, Severity Grading, and Reporting

### 13.1.1 Adverse Events

#### 13.1.1.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or worsening of a pre-existing condition (e.g., increase in its severity or frequency) after the ICF is signed.

An AE is considered serious if it meets the definition in Section 13.1.2.1.

#### 13.1.1.2 Clinically Significant Assessments

Study assessments including laboratory tests, PEs, pulse oximetry, and vital signs will be assessed and those deemed to have clinically-significant worsening from baseline will be documented as an AE. When possible, a clinical diagnosis for the study assessment will be provided, rather than the abnormal test result alone (e.g., hepatitis). In the absence of a diagnosis, the abnormal study assessment itself will be listed as the AE (e.g., elevated ALT).

An abnormal study assessment is considered clinically significant if the subject has 1 or more of the following:

- Concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention
- A change in the dose of study drug or discontinuation from the study

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant will be made by the investigator.

A laboratory value that is Grade 4 will not automatically be an SAE. A Grade 4 laboratory value will be an SAE if the subject's clinical status indicates a life-threatening AE.

#### 13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time ICF and assent (where applicable) is signed until the following time points:

- For subjects who do not enroll: until time of screen failure or withdrawal of consent
- For enrolled subjects who complete the study and for subjects who prematurely discontinue study drug and have a Safety Follow-up Contact: through the Safety Follow-up Contact
- For enrolled subjects who prematurely discontinue study drug (including for withdrawal of consent) and do not have Safety Follow-up Contact, the earliest of:
    - 28 days after the last dose of study drug, or

- the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (see Section 9.1.4)

All subjects will be queried, using nonleading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms will be identified as 1 overall event or diagnosis. All AEs for enrolled subjects will be recorded in the CRF and source document. AEs for subjects who are screened but not subsequently enrolled in the study will be recorded only in the subject's source documents. The following data will be documented for each AE:

- Description of the event
- Classification of "serious" or "nonserious"
- Date of first occurrence and date of resolution (if applicable)
- Severity
- Causal relationship to study drug(s)
- Action taken
- Outcome
- Concomitant medication or other treatment given

#### 13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." In considering the severity of an AE in a pediatric subject, the investigator will consider that reference ranges for pediatric clinical laboratory parameters may differ from those given in the CTCAE. The severity of an AE that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

**Table 13-1 Grading of AE Severity**

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

#### 13.1.1.5 Adverse Event Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug(s). Causality will be classified using the categories presented in Table 13-2.

**Table 13-2 Classifications for AE Causality**

| Classification | Definition |
|---|---|
| **Related** | There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event reappeared on re-exposure to the investigational study drug. |
| **Possibly related** | There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease. |
| **Unlikely related** | The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug. |
| **Not related** | The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the study subject's medical record). |

#### 13.1.1.6 Study Drug Action Taken

The investigator will classify the study drug action taken with regard to the AE. The action taken will be classified according to the categories shown in Table 13-3.

**Table 13-3 Classifications for Study Drug Action Taken With Regard to an AE**

| Classification | Definition |
|---|---|
| **Dose not changed** | Study drug dose not changed in response to an AE |
| **Dose reduced** | Study drug dose reduced in response to an AE |
| **Drug interrupted** | Study drug administration interrupted in response to an AE |
| **Drug withdrawn** | Study drug administration permanently discontinued in response to an AE |
| **Not applicable** | Action taken regarding study drug administration does not apply.<br>"Not applicable" will be used in circumstances such as when the investigational treatment had been completed before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible. |

#### 13.1.1.7 Adverse Event Outcome

An AE will be followed until the investigator has determined and provided the final outcome. The outcome will be classified according to the categories shown in Table 13-4.

**Table 13-4 Classifications for Outcome of an AE**

| Classification | Definition |
|---|---|
| **Recovered/resolved** | Resolution of an AE with no residual signs or symptoms |
| **Recovered/resolved with sequelae** | Resolution of an AE with residual signs or symptoms |
| **Not recovered/not resolved (continuing)** | Either incomplete improvement or no improvement of an AE, such that it remains ongoing |
| **Fatal** | Outcome of an AE is death. "Fatal" will be used when death is at least possibly related to the AE. |
| **Unknown** | Outcome of an AE is not known (e.g., a subject lost to follow-up) |

#### 13.1.1.8 Treatment Given

The investigator ensures adequate medical care is provided to subjects for any AEs, including clinically significant laboratory values related to study drug. In addition, the investigator will describe whether any treatment was given for the AE. "Yes" is used if any treatment was given in response to an AE, and may include treatments such as other medications, hospitalization, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

### 13.1.2 Serious Adverse Events

#### 13.1.2.1 Definition of a Serious Adverse Event

An SAE is any AE that meets any of the following outcomes:

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation in the study and is suspected of being a delayed toxicity due to administration of the study drug)
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Congenital anomaly or birth defect
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home)

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the subject signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure will not be considered to indicate an SAE, unless an AE caused the hospitalization or procedure to be rescheduled sooner or to be prolonged relative to what was planned. In addition, hospitalizations clearly not associated with an AE (e.g., social hospitalization for purposes of respite care) will not be considered to indicate an SAE.

Clarification will be made between the terms "serious" and "severe" because they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event, as in mild, moderate, or severe myocardial infarction. The event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on subject/event outcome or action described above, and is usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining expedited regulatory reporting obligations.

#### 13.1.2.2 Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through the Safety Follow-up Contact, regardless of causality, will be reported by the investigator to Vertex

GPS. In addition, all SAEs that occur after the Safety Follow-up Contact and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours**.

SAEs will be recorded on the Vertex Organized Safety Information Collection Form (hereafter referred to as the "SAE Form") using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for relationship to the investigational study drug(s) and possible etiologies. On the SAE Form, relationship to study drug(s) will be assessed only as related (includes possibly related) or not related (includes unlikely related), and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report to Vertex the outcome of the event using the SAE Form.

#### 13.1.2.3 Reporting Serious Adverse Events

The investigator is responsible for notifying the sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. The SAE Form will be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

Contact Telephone: [redacted]

#### 13.1.2.4 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions involving the study drug(s) to all regulatory authorities and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to central IECs.

It is the responsibility of the investigator or designee to promptly notify the local IRB/local IEC of all unexpected serious adverse drug reactions involving risk to human subjects.

### 13.2 Administrative Requirements

#### 13.2.1 Ethical Considerations

The study will be conducted in accordance with the current ICH GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local applicable laws and regulations. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

### 13.2.2 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject or legal representative or guardian (if applicable), and assent will be obtained from the subject (if applicable), before study participation. The method of obtaining and documenting the informed consent and assent (if applicable) and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

### 13.2.3 Investigator Compliance

No modifications to the protocol will be made without the approval of both the investigator and Vertex. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (i.e., efficacy assessments) will require IRB/IEC notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. Vertex will submit all protocol modifications to the required regulatory authorities.

When circumstances require an immediate departure from procedures set forth in the protocol, the investigator will contact Vertex to discuss the planned course of action. If possible, contact will be made before the implementation of any changes. Any departures from the protocol will be fully documented in the source documentation and in a protocol deviation log.

### 13.2.4 Access to Records

The investigator will make the office and/or hospital records of subjects enrolled in this study available for inspection by Vertex or its representative at the time of each monitoring visit and for audits. The records will also be available for direct inspection, verification, and copying, as required by applicable laws and regulations, by officials of the regulatory health authorities (FDA and others). The investigator will comply with applicable privacy and security laws for use and disclosure of information related to the research set forth in this protocol.

### 13.2.5 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all CRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers and access to subject names linked to such numbers shall be limited to the site and the study physician and shall not be disclosed to Vertex. As required by applicable laws and regulations in the countries in which the study is being conducted, the investigator will allow Vertex and/or its representatives access to all pertinent medical records to allow for the verification of data gathered in the CRFs/SAE forms and the review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/IEC, may also request access to all study records, including source documentation, for inspection.

### 13.2.6 Record Retention

The investigator will maintain all study records according to ICH GCP guidelines and/or applicable local regulatory requirement(s), whichever is longest, as described in the Clinical Trial Agreement. If the investigator withdraws from the responsibility of keeping the study records, custody will be transferred to a person willing to accept the responsibility and Vertex will be notified.

### 13.2.7 Study Termination

At any time, Vertex may terminate this study in its entirety or may terminate this study at any particular site. In addition, for reasonable cause, either the investigators or their IRBs/IECs may terminate the study at their center.

Conditions that may lead to reasonable cause and warrant termination include, but are not limited to:

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the FDA or other regulatory authority

Written notification that includes the reason for the clinical study termination is required.

## 13.3 Data Quality Assurance

Vertex or its designated representative will conduct a study site visit to verify the qualifications of each investigator, inspect clinical study site facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure, validated web-based electronic data capture (EDC) application. Vertex will have read-only access to site-entered clinical data in the EDC application.

Instances of missing, discrepant, or uninterpretable data will be queried with the investigator for resolution. Any changes to study data will be made to the CRF and documented in an audit trail, which will be maintained within the clinical database.

## 13.4 Monitoring

Monitoring and auditing procedures developed or approved by Vertex will be followed to comply with GCP guidelines. On-site checking of the CRFs/SAE Forms for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by Vertex or its designee. Monitoring will be done by personal visits from a representative of Vertex, or designee (study site monitor), who will review the CRFs/SAE Forms and source documents. The study site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

## 13.5 Electronic Data Capture

Vertex will provide the study sites with secure access to and training on the EDC application sufficient to permit study site personnel to enter or correct information in the eCRFs on the subjects for which they are responsible.

An eCRF will be completed for each enrolled study subject. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data will indicate the subject's participation in the study and will document the dates and details of study procedures, AEs, other observations, and subject status.

The investigator, or designated representative, will complete the eCRF as soon as possible after information is collected.

The audit trail entry will show the user's identification information and the date and time of any correction. The investigator must provide formal approval of all the information in the eCRFs, including any changes made to the eCRFs, to endorse the final submitted data for the subjects for whom the investigator is responsible.

Vertex will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disc or other electronic media will be placed in the investigator's study file.

## 13.6 Publications and Clinical Study Report

[redacted]

### 13.6.2 Clinical Study Report

A clinical study report, written in accordance with the ICH E3 Guideline, will be submitted in accordance with local regulations.

## 14 REFERENCE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5 Vertex Pharmaceuticals Incorporated. Ivacaftor (VX-770) Investigator's Brochure, Version 13.0. Report date: 16 May 2016.

6 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.

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10 Wenninger K, Aussage P, Wahn U, Staab D, German Cystic Fibrosis Questionnaire study group. The revised German Cystic Fibrosis Questionnaire: validation of a disease-specific health-related quality of life instrument. Qual Life Res. 2003;12(1):77-85.

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# 15 PROTOCOL SIGNATURE PAGES

## 15.1 Sponsor Signature Page

| Protocol #: VX16−661−114 | Version #: 3.1 US | Version Date: 09 June 2017 |
|---|---|---|
| Study Title: Phase 3b, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Safety, Efficacy, and Tolerability of Tezacaftor/Ivacaftor (TEZ/IVA) in an Orkambi-experienced Population Who Are Homozygous for the *F508del-CFTR* Mutation | | |

This Clinical Study Protocol has been reviewed and approved by the sponsor.

[redacted]

## 15.2 Investigator Signature Page

| Protocol #: VX16−661−114 | Version #: 3.1 US | Version Date: 09 June 2017 |
|---|---|---|
| Study Title: Phase 3b, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Safety, Efficacy, and Tolerability of Tezacaftor/Ivacaftor (TEZ/IVA) in an Orkambi-experienced Population Who Are Homozygous for the *F508del-CFTR* Mutation | | |

I have read Protocol VX16-661-114, Version 3.1 US, and agree to conduct the study according to its terms. I understand that all information concerning TEZ and IVA and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date