# 1 TITLE PAGE

*VERTEX PHARMACEUTICALS INCORPORATED*

# Clinical Study Protocol

**A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Tezacaftor in Combination With Ivacaftor in Subjects With Cystic Fibrosis Aged 6 Years and Older, Homozygous or Heterozygous for the *F508del-CFTR* Mutation**

**Vertex Study Number: VX17-661-116**

[redacted]

**EudraCT Number: 2017-002968-40**

**Date of Protocol:** 08 Nov 2019 (Version 2.3 US)

Replaces Version 1.0 (dated 08 December 2017)

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# 2 PROTOCOL SYNOPSIS

**Title** A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Tezacaftor in Combination With Ivacaftor in Subjects With Cystic Fibrosis Aged 6 Years and Older, Homozygous or Heterozygous for the *F508del-CFTR* Mutation

**Brief Title** A Study to Evaluate the Safety and Efficacy of Long-term Treatment With TEZ/IVA in CF Subjects With an *F508del-CFTR* Mutation

**Clinical Phase and Clinical Study Type** Phase 3, safety and efficacy

**Objectives**

**Primary Objective**

To evaluate the long-term safety and tolerability of tezacaftor in combination with ivacaftor (TEZ/IVA) in subjects with cystic fibrosis (CF) aged 6 years and older, homozygous or heterozygous for the *F508del* mutation

**Secondary Objective**

To evaluate the long-term efficacy of TEZ/IVA in subjects with CF aged 6 years and older, homozygous or heterozygous for the *F508del* mutation

**Endpoints**

**Primary Endpoint**

Safety and tolerability of long-term TEZ/IVA treatment based on adverse events (AEs), clinical laboratory values (serum chemistry, hematology, lipids, and vitamins), standard 12-lead ECGs, physical examinations (PEs), vital signs, ophthalmologic examinations, and pulse oximetry

**Secondary Endpoints**

- Absolute change from baseline in lung clearance index$_{2.5}$ (LCI$_{2.5}$; for subjects from Study VX16-661-115 [Study 115] and the Study VX15-661-113 Part B [Study 113B] LCI Substudy only)
- Absolute change from baseline in sweat chloride
- Absolute change from baseline in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score
- Absolute change from baseline in body mass index (BMI)

[redacted]

[redacted]

**Number of Subjects**

Study VX17-661-116 is a rollover study.

Approximately 56 subjects from Study 113B and 65 subjects from Study 115 are potentially eligible for enrollment. Up to approximately 121 subjects are potentially eligible for enrollment.

**Study Population**

Male and female subjects with CF aged 6 years and older, who completed Study 113 B or Study 115 and are

- homozygous for *F508del* (F/F),
- heterozygous for *F508del* and a second allele with a residual CFTR-function mutation (F/RF), or
- heterozygous for *F508del* and a second allele that has been shown to be responsive to TEZ/IVA

**Investigational Drug**

**Active substance:** TEZ and IVA

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

**Strength and route of administration:** TEZ 50-mg/IVA 75-mg fixed-dose combination (FDC) tablet or TEZ 100-mg/IVA 150-mg FDC tablet; oral administration

**Active substance:** IVA

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

**Strength and route of administration:** IVA 75- or 150-mg tablet; oral administration

**Study Design**

This is a Phase 3, multicenter, open-label, rollover study in subjects with CF who are homozygous or heterozygous for *F508del* and who completed the Week 24 Visit in Study 113B or the Week 8 Visit in Study 115. The study is designed to evaluate the safety and efficacy of long-term TEZ/IVA treatment in pediatric subjects aged 6 years and older.

During the course of study conduct, if TEZ/IVA receives marketing authorization and is available for the treatment of CF in populations enrolled in this study, subjects with the approved *CFTR* genotypes may be discontinued from this rollover study at the discretion of the sponsor. If a subject continues onto a commercially available Vertex CFTR modulator, the Early Treatment Termination (ETT) Visit will be completed before dosing with commercial drug begins, and the Safety Follow-up Visit will not be required.

If a subject is continuing onto TEZ/IVA supplied via a Vertex-sponsored managed access program (MAP), the ETT Visit will be completed before dosing with TEZ/IVA via the MAP, and the Safety Follow-up Visit will not be required.

Alternatively, if local health authorities decline to grant marketing authorization, or if clinical benefit is not demonstrated for the use of TEZ/IVA for the treatment of CF in populations enrolled in this study, subjects with the relevant *CFTR* genotypes

may be discontinued after communication to investigators and IRBs/IECs of the risks/benefits related to the safety and efficacy observed for the subset of subjects. If subjects are discontinued from the study, an ETT Visit should occur within 7 days of the last dose of study drug and a Safety Follow-up Visit should occur within 28 (± 7) days after the last dose of study drug.

**Assessments**

**Safety Assessments**

AEs, clinical laboratory values (serum chemistry, hematology, lipids, and vitamins), standard 12-lead ECGs, vital signs, pulse oximetry, PEs, and ophthalmologic examinations

**Efficacy Assessments**

LCI, [redacted] sweat chloride, CFQ-R, weight, height, BMI, [redacted]

**Statistical Analyses**

Statistical analysis details will be provided in the statistical analysis plan (SAP), which will be finalized before the clinical database lock for the study.

The safety analysis will be performed on all subjects in the Safety Set. The efficacy analysis will be performed on all subjects in the Full Analysis Set for each parent study respectively. The methods used for the efficacy analyses will be similar for those used in the parent studies.

The least square (LS) mean and the associated 95% CI at each defined analysis visit will be provided for the corresponding efficacy endpoints. Descriptive summary statistics will be provided for relevant safety and efficacy parameters.

Interim analyses (IAs) may occur at any time during the study. The timing and IA analysis plans will be documented in the SAP.

**IDMC Reviews**

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

# 3 SCHEDULE OF ASSESSMENTS

The Schedule of Assessments is shown in **Error! Reference source not found.**.

**Table 3-1 Study VX17-661-116: Treatment Period and Safety Follow-up Visit**

| Event/Assessment[a] | Treatment Period | | | | ETT Visit[b,c] | Safety Follow-up Visit 28 (±7) Days After Last Study Drug Dose[b,c] |
|---|---|---|---|---|---|---|
| | Day 1[d] | *Study 115 Subjects Only* Day 15 (± 3 days) | *Study 115 Subjects Only* Week 4 (±7 days) | Weeks 12, 24, 36, 48, 60, 72, 84, and 96 (±7 days) | | |
| Clinic visit | X | X | X | X | X | X |
| Informed consent/assent | X | | | | | |
| Inclusion and exclusion criteria review | X | | | | | |
| *CFTR* genotype[e] | X | | | | | |
| CFQ-R[f] | X | X | X | X | X | |
| Height and weight[g] | X | X | X | X | X | X |
| Ophthalmologic examination[h] | X[i] | | | Weeks 48 and 96[j] | X[k] | X[i,k] |

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

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

[c] If a subject is continuing onto a commercially available Vertex CFTR modulator, or if the subject will receive TEZ/IVA via a Vertex-sponsored managed access program (MAP), the ETT Visit will be completed before dosing with commercial drug or MAP drug begins, and the Safety Follow-up Visit will not be required.

[d] The Day 1 Visit of Study 116 may be on the **same day** as the last scheduled visit of the parent study; this will occur at the Week 24 Visit for subjects from Study 113B and at the Week 8 Visit for subjects from Study 115. Subjects will NOT have to repeat any Study 116 Day 1 assessments that were specified to be performed at the last scheduled visit in the parent study. For subjects who were enrolled in Study 116, but had Day 1 study drug administration procedures delayed, Section 9.1.1 describes the assessments to be performed on Day 1.

[e] The *CFTR* genotype result can be taken from Study 113 or Study 115. If the genotype result is not available, subjects will be tested for *CFTR* genotype; if the genotype result from the confirmatory test is exclusionary, then the subject will be removed from the study.

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

[g] Height and weight will be measured with shoes off and before dosing with study drug. BMI will be derived from height and weight.

[h] Ophthalmologic examinations will be performed by a licensed ophthalmologist or optometrist.

[i] Subjects who did not have an ophthalmologic examination at the end of Study 113B or Study 115 will have an ophthalmologic examination at the Day 1 Visit, or no more than 28 days after. Subjects who had an ophthalmological examination in the parent study less than 28 days before Day 1 of Study 116 do not need to repeat the examination.

[j] An ophthalmologic examination will occur either at the Week 96 Visit (± 28 days) or the Safety Follow-up Visit, but must be completed by the date of the Safety Follow-up Visit.

[k] Subjects who discontinue treatment after receiving at least 1 dose of study drug will have an ophthalmologic examination. The examination may be completed at either the ETT or Safety Follow-up Visit, but must be completed by the date of the Safety Follow-up Visit.

## Table 3-1 Study VX17-661-116: Treatment Period and Safety Follow-up Visit

| Event/Assessment[a] | Treatment Period | | | | ETT Visit[b,c] | Safety Follow-up Visit 28 (±7) Days After Last Study Drug Dose[b,c] |
|---|---|---|---|---|---|---|
| | Day 1[d] | *Study 115 Subjects Only* Day 15 (± 3 days) | *Study 115 Subjects Only* Week 4 (±7 days) | Weeks 12, 24, 36, 48, 60, 72, 84, and 96 (±7 days) | | |
| Complete physical examination[l] | X | | | Week 96 | X | X |
| Standard 12-lead ECG[m] | X | | | Weeks 24, 48, 72, and 96 | X | X |
| Pregnancy test[n] | X | | | Weeks 24, 48, 72, and 96 | X | X |
| Vital signs[o] | X | X | X | X | X | X |
| Pulse oximetry[o] | X | X | X | X | X | X |
| MBW[p] (Study 113B LCI Substudy and Study 115 subjects only) | X | X | X | Weeks 24, 48, 72, and 96 | X | |
| [redacted] | | | | | | |
| Hematology | X[r] | X | | X | X | X |
| Serum chemistry | X[r] | X | | X | X | X |
| Lipid panel | X[r] | | | Weeks 24, 48, 72, and 96 | X | X |
| Vitamin levels | X[r] | | | Weeks 24, 48, 72, and 96 | X | X |
| [redacted] | | | | | | |

Symptom-directed physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

m All standard 12-lead ECGs will be performed before dosing and after the subject has been supine for at least 5 minutes. ECGs collected on Day 1 before dosing will be performed in triplicate.

n Serum pregnancy tests will be performed at the site for all female subjects of childbearing potential. All pregnancy tests will be serum tests, except for the Day 1 Visit, when a urine pregnancy test will be performed at the site and results reviewed before dosing with study drug.

o Vital signs and pulse oximetry will be collected before dosing and after the subject has been at rest for at least 5 minutes.

p The MBW assessment will be performed on multiple replicates and before study drug dosing (see Section 11.3.1 and the Study Reference Manual). MBW should be performed pre-bronchodilator [redacted]

r Blood samples should be collected before the first dose of study drug on Day 1. Blood sampling for all other clinical visits except the Day 1 Visit may be conducted at any time after the ECG assessment and before the snack or meal.

[redacted]

## Table 3-1 Study VX17-661-116: Treatment Period and Safety Follow-up Visit

| Event/Assessment[a] | Treatment Period: Day 1[d] | Treatment Period: *Study 115 Subjects Only* Day 15 (± 3 days) | Treatment Period: *Study 115 Subjects Only* Week 4 (±7 days) | Treatment Period: Weeks 12, 24, 36, 48, 60, 72, 84, and 96 (±7 days) | ETT Visit[b,c] | Safety Follow-up Visit 28 (±7) Days After Last Study Drug Dose[b,c] |
|---|---|---|---|---|---|---|
| Sweat chloride[t] | X | | | Weeks 24, 48, and 96 | X | |
| [redacted] | | | | | | |
| Meal(s) or snack(s) at site[v] | X | X | X | X[w] | | |
| Study drug count | | X | X | X | X | |
| Study drug dosing[x] | *Day 1 to Week 96* | | | | | |
| Medications review | *Continuous from signing of the ICF and assent (where applicable) through the Safety Follow-up Visit* | | | | | |
| Treatment and procedures review | *Continuous from signing of the ICF and assent (where applicable) through the Safety Follow-up Visit* | | | | | |
| AEs and SAEs[y] | *Continuous from signing of the ICF and assent (where applicable) through the Safety Follow-up Visit* | | | | | |

AE: adverse event; BMI: body mass index; CF: cystic fibrosis; CFQ-R: CF Questionnaire–Revised; ETT: Early Treatment Termination; ICF: informed consent form; IVA: ivacaftor; LCI: lung clearance index; MBW: multiple-breath washout; SAE: serious adverse event; TEZ: tezacaftor

[t] No other assessments should overlap with sweat chloride collection.

[redacted]

[v] A fat-containing meal or snack will be provided at the site to subjects after all predose assessments have occurred.

[w] Providing a meal or snack is optional at the Week 96 Visit.

[x] The study drug should be administered every 12 hours (± 2 hours) within 30 minutes after starting a meal with fat-containing food. On days of scheduled visits, the morning dose of study drug will be administered at the site after the predose assessments have been completed. The final dose of study drug will be administered the evening before the Week 96 Visit.

[y] SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be reported to Vertex Global Patient Safety **within 24 hours** as described in Section 13.1.2.3

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## List of Abbreviations

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine transaminase |
| AST | aspartate transaminase |
| β-hCG | beta-human chorionic gonadotropin |
| BMI | body mass index |
| BPM | beats per minute |
| CD | compact disc |
| CF | cystic fibrosis |
| CFQ-R | Cystic Fibrosis Questionnaire-Revised |
| CFTR | CF transmembrane conductance regulator protein |
| *CFTR* | CF transmembrane conductance regulator gene |
| CI | confidence interval |
| $Cl^-$ | chloride ion |
| CRF | case report form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | cytochrome P450 |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EENT | eyes, ears, nose, and throat |
| ETT | Early Termination of Treatment |
| *F508del* | *CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FDC | fixed-dose combination |
| $FEV_1$ | forced expiratory volume in 1 second |
| F/F | homozygous for *F508del* |
| F/RF | heterozygous for *F508del* and a second mutation that results in residual CFTR function |
| [redacted] | [redacted] |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GLI | Global Lung Function Initiative |
| GPS | Global Patient Safety |
| HDL | high-density lipoprotein |
| HIPAA | Health Insurance Portability and Accountability Act |
| HR | heart rate |
| IA | interim analysis |
| ICF | informed consent form |
| ICH | International Council for Harmonization |

| Abbreviation | Definition |
|---|---|
| IDMC | independent data monitoring committee |
| IEC | independent ethics committee |
| IRB | institutional review board |
| [redacted] | [redacted] |
| IV | intravenous |
| IVA | ivacaftor |
| LCI | lung clearance index |
| $LCI_{2.5}$ | number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value |
| [redacted] | [redacted] |
| LDL | low-density lipoprotein |
| LFT | liver function test |
| LS | least square |
| MAP | managed access program |
| max | maximum value |
| MBW | multiple-breath washout |
| MedDRA | Medical Dictionary for Regulatory Activities |
| min | minimum value |
| MMRM | mixed-effects model for repeated measures |
| n | number of subjects |
| PE | physical examination |
| [redacted] | [redacted] |
| P-gp | P-glycoprotein |
| PI | principal investigator |
| [redacted] | [redacted] |
| PR | PR interval, segment |
| PT | Preferred Term |
| q12h | every 12 hours |
| qd | daily |
| QRS | the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization |
| QT | QT interval |
| QTc | QT interval corrected |
| QTcF | QT interval corrected by Fridericia's formula |
| *R117H* | *CFTR* missense gene mutation that results in the replacement of an arginine residue at position 117 of CFTR with a histidine residue |
| RR | interval from the onset of 1 QRS complex to the next |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SE | standard error |
| SET | study execution team |
| SI | SI units (International System of Units) |

| Abbreviation | Definition |
|---|---|
| SOC | System Organ Class |
| SUSARs | suspected, unexpected, serious adverse reaction |
| TE | treatment emergent |
| TEAE | treatment-emergent adverse event |
| TEZ | tezacaftor |
| TEZ/IVA | tezacaftor in combination with ivacaftor |
| ULN | upper limit of normal |
| US | United States |
| USA | United States of America |
| WHO-DDE | World Health Organization-Drug Dictionary Enhanced |

# 5 INTRODUCTION

## 5.1 Background

Cystic fibrosis (CF) affects an estimated 70,000 children and adults worldwide.[1] CF is a progressive, systemic, life-shortening, genetic disease that is caused by reduced quantity and/or function of the CFTR protein due to mutations in the *CFTR* gene. In people with CF, loss of chloride transport due to defects in CFTR result in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction, and elevated sweat chloride concentration. Lung disease is the primary cause of morbidity and mortality in people with CF. The median predicted age of survival of individuals born today with CF is approximately 40 years of age.[1, 2]

Two complementary approaches to increase CFTR-mediated $Cl^-$ secretion in the airway epithelia have been studied.[3] One approach is to treat with a compound that will modify the cellular processing and trafficking of the CFTR protein to increase the amount of functional CFTR at the cell surface. This kind of compound has been termed a CFTR corrector. Another approach is to treat with a compound that increases the channel gating activity of CFTR at the cell surface to enhance ion transport. This kind of compound has been termed a potentiator.

Tezacaftor (TEZ) and ivacaftor (IVA) are CFTR modulators with interdependent mechanisms of action in treating CF patients with CFTR mutations that require a combination therapy approach. TEZ and IVA both address the underlying cause of CF, and each has a different and essential role as a corrector (TEZ) or potentiator (IVA) of the CFTR protein in CF patients.

TEZ (VX-661) and IVA (VX-770) were developed by Vertex Pharmaceuticals Incorporated (Vertex). TEZ/IVA combination therapy (trade names Symdeko™ and Symkevi™) is indicated for the treatment of CF in patients as young as 6 years of age homozygous for *F508del* or who have another indicated *CFTR* genotype. IVA monotherapy (Kalydeco™) is indicated for the treatment of CF in patients as young as 2 years old with specific *CFTR* mutations including certain gating mutations as well the *R117H* mutation. The indicated mutations and approved populations for Symdeko/Symkevi and Kalydeco vary by country. Please refer to local prescribing information or summary of product characteristics for your region for the current approved use of Symdeko/Symkevi and Kalydeco.

Results from 2 pivotal Phase 3 Studies, VX14-661-106 (Study 106) and VX14-661-108 (Study 108), that evaluated TEZ in combination with IVA (TEZ/IVA) demonstrated clinically meaningful and statistically significant improvements in lung function and key secondary endpoints along with favorable safety and benefit/risk profiles with the TEZ daily (qd)/IVA every 12 hours (q12h) regimen in CF subjects homozygous for *F508del* (F/F), or heterozygous for *F508del* and a second mutation that results in residual CFTR function (F/RF), aged ≥12 years.

Additional details about TEZ/IVA can be found in the TEZ/IVA Investigator's Brochure.

## 5.2 Study Rationale

To date, the long-term safety of TEZ/IVA has not yet been evaluated in subjects with CF aged 6 to 11 years. Therefore, the primary objective of this study is to evaluate the long-term safety and tolerability of TEZ/IVA in subjects with CF in this age group, who are homozygous or

heterozygous for *F508del*. The secondary objective is to evaluate the long-term efficacy of treatment with TEZ/IVA.

This study will enroll subjects who completed Studies VX15-661-113 Part B (Study 113B) or VX16-661-115 (Study 115). In both parent studies, subjects were 6 to 11 years of age at Screening and are homozygous or heterozygous for *F508del*.

# 6 STUDY OBJECTIVES

## 6.1 Primary Objective

To evaluate the long-term safety and tolerability of TEZ/IVA in subjects with CF aged 6 years and older, who are homozygous or heterozygous for *F508del*

## 6.2 Secondary Objective

To evaluate the long-term efficacy of TEZ/IVA in subjects with CF aged 6 years and older, who are homozygous or heterozygous for *F508del*

# 7 STUDY ENDPOINTS

## 7.1 Primary Endpoint

Safety and tolerability of long-term TEZ/IVA treatment based on adverse events (AEs), clinical laboratory values (serum chemistry, hematology, lipids, and vitamins), standard 12-lead ECGs, physical examinations (PEs), vital signs, ophthalmologic examinations, and pulse oximetry

## 7.2 Secondary Endpoints

- Absolute change from baseline in lung clearance index$_{2.5}$ (LCI$_{2.5}$; for subjects from Study 115 and the Study 113B LCI Substudy only)
- Absolute change from baseline in sweat chloride
- Absolute change from baseline in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score
- Absolute change from baseline in body mass index (BMI)

[redacted]

[redacted]

# 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's legally appointed and authorized representative will sign and date an informed consent form (ICF) and the subject will sign an assent form (if applicable).
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Completed the Week 24 Visit in Study 113B or the Week 8 Visit in Study 115.

Added guidance:

- Subjects who had a study drug interruption at the last scheduled visit of Study 113B or Study 115, subjects who required study drug interruption that was to be continued or initiated at Day 1 in Study 116, or subjects who resumed study drug in the parent study after a study drug interruption due to elevated transaminases, but who did not complete at least 4 weeks of rechallenge with study drug (due to the timing of the rechallenge versus the time remaining in the parent study), must receive approval from the Vertex medical monitor.

  Note: Subjects who permanently discontinue study drug treatment during the parent study, including at the last visit of the Treatment Period, are not eligible.

4. Did not withdraw consent from the parent study.
5. Subjects must have a genotype listed in Appendix 1: *CFTR* Mutations. Note: Additional mutations may be evaluated and updates to the list of eligible mutations will be communicated to investigative sites through a memorandum. If TEZ/IVA receives marketing authorization for additional mutations in any country/region for patients ≥12 years old, a memorandum will be sent to investigative sites in that country/region and the newly approved mutations will also be eligible.
6. Willing to remain on a stable CF medication regimen through the Safety Follow-up Visit.

## 8.2 Exclusion Criteria

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.

   For example, history of cirrhosis with portal hypertension, and/or history of risk factors for Torsade de Pointes (e.g., familial long QT syndrome, hypokalemia, heart failure, left ventricular hypertrophy, bradycardia, myocardial infarction, cardiomyopathy, history of arrhythmia [ventricular and atrial fibrillation], obesity, acute neurologic events [subarachnoid hemorrhage, intracranial hemorrhage, cerebrovascular accident, and intracranial trauma], and autonomic neuropathy).

2. Pregnant and nursing females. Females of childbearing potential must have a negative pregnancy test at the Day 1 Visit before receiving the first dose of study drug (Section 11.4.2).

3. Sexually active subjects of reproductive potential who are not willing to follow the contraception requirements outlined in Section 11.4.8.

4. History of drug intolerance in the parent study that would pose an additional risk to the subject in the opinion of the investigator, and which should be discussed with the Vertex medical monitor. Examples of subjects who may not be eligible for the study include (but are not limited to) the following:

   - Subjects with a history of allergy or hypersensitivity to the study drug
   - Liver function test (LFT) abnormality during study drug treatment in the parent study or other qualified Vertex study that required permanent study drug discontinuation
   - Other severe or life-threatening reactions to the study drug in the previous study

5. History of poor compliance with study drug and/or procedures in a previous study as deemed by the investigator.

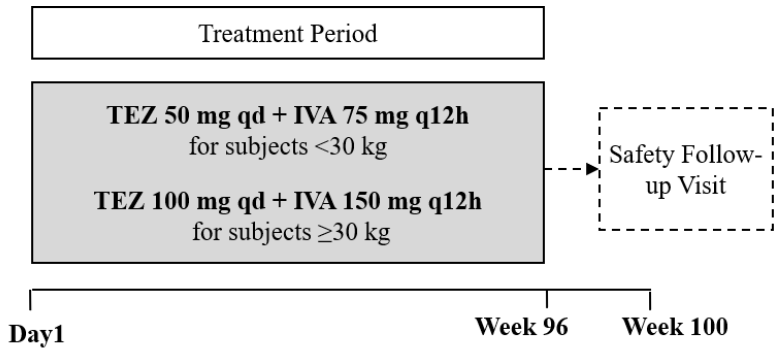
6. Ongoing participation in another study with investigational drug. Ongoing participation in a non-interventional study (including observational studies) is permitted. During the Treatment Period, subjects may screen for another Vertex-sponsored study of CFTR modulators, excluding studies of IVA monotherapy and lumacaftor in combination with IVA. If a subject chooses to enroll in the other Vertex-sponsored study, they will be terminated from Study 116 and will not be allowed to re-enroll in Study 116.

# 9 STUDY IMPLEMENTATION

## 9.1 Study Design

This is a Phase 3, open-label, rollover study. A schematic of the study design is shown in Figure 9-1.

**Figure 9-1 VX17-661-116 Study Design**




IVA: ivacaftor, q12h: every 12 hours, qd: daily, TEZ: tezacaftor

### 9.1.1 Treatment Period

Treatment Period assessments are listed in Table 3-1.

The Day 1 Visit of Study 116 will be on the **same day** as the last scheduled visit of the parent study; this will occur at the Week 24 Visit for subjects from Study 113B and at the Week 8 Visit for subjects from Study 115. Subjects will NOT have to repeat any Study 116 Day 1 Visit assessments that were specified to be performed at the last scheduled visit in the parent study.

Subjects who were enrolled in Study 116, but had Day 1 study drug administration procedures delayed (e.g., due to an AE), will repeat the safety, LCI (if applicable), [redacted] assessments that were specified to be performed at the Day 1 Visit before receiving their first dose of study drug.

For subjects at Study 116 sites that have NOT been activated by the time the subject has completed the last scheduled visit in the parent study, the Day 1 Visit of Study 116 will NOT coincide with the last scheduled visit of the parent study. Subjects at these sites with delayed activation will have to repeat any Study 116 Day 1 assessments that were specified to be performed at the last scheduled visit in the parent study.

All subjects will have study visits on Day 1 and at Weeks 12, 24, 36, 48, 60, 72, 84, and 96.

***Study Visits on Day 15 and Week 4 are only required for subjects from Study 115.***

### 9.1.2 Safety Follow-up

Subjects will have a Safety Follow-up Visit 28 (±7) days after the last dose of study drug. Safety Follow-up Visit assessments are listed in Table 3-1.

If a subject chooses to continue onto a commercially available Vertex CFTR modulator (i.e., TEZ/IVA [if approved for marketing], Kalydeco, Orkambi™ [lumacaftor/IVA], or another approved TEZ/IVA-containing regimen), the Early Termination of Treatment (ETT) Visit will be completed before dosing with the commercial drug begins, and the Safety Follow-up Visit will not be required.

If a subject is continuing onto TEZ/IVA supplied via a Vertex-sponsored managed access program (MAP), the ETT Visit will be completed before dosing with TEZ/IVA via the MAP, and the Safety Follow-up Visit will not be required (see Section 9.1.3).

### 9.1.3 Early Termination of Treatment

If the subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the subject/caregiver decides to terminate study treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (± 7) days after their last dose of study drug.

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

If a subject chooses to continue onto a commercially available Vertex CFTR modulator (i.e., TEZ/IVA [Symdeko], Kalydeco, Orkambi™, or another approved TEZ/IVA-containing drug), the ETT Visit will be completed before dosing with the commercial drug begins, and the Safety Follow-up Visit (Section 9.1.2) will not be required.

If a subject is continuing onto TEZ/IVA supplied via a Vertex-sponsored managed access program (MAP), the ETT Visit will be completed before dosing with TEZ/IVA via the MAP, and the Safety Follow-up Visit will not be required.

Alternatively, if local health authorities decline to approve, or if clinical benefit is not demonstrated for the use of TEZ/IVA for the treatment of CF in populations enrolled in Study 116, subjects with the relevant *CFTR* genotypes may be discontinued after communication to investigators and IRBs/IECs of the risks/benefits related to the safety and efficacy observed for the subset of subjects concerned. If subjects are discontinued from the study, an ETT Visit should occur within 7 days of the last dose of study drug and a Safety Follow-up Visit should occur within 28 (± 7) days after the last dose of study drug.

If the subject/caregiver withdraws consent for the study, no further evaluations should be performed, and no additional data should be collected. Vertex may retain and continue to use any data and samples collected before such withdrawal of consent.

### 9.1.4 Independent Data Monitoring Committee

Safety and tolerability data will be reviewed by an independent data monitoring committee (IDMC) to ensure the safety of the subjects in the study (Section 12.3.5.2). 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 enrolled.

## 9.2 Method of Assigning Subjects to Treatment Groups

This is an open-label study. Randomization is not required.

## 9.3 Rationale for Study Design and Study Drug Regimens

### 9.3.1 Study Design

This is a Phase 3, multicenter, open-label, rollover study in subjects with CF aged 6 years and older, who are homozygous or heterozygous for *F508del,* and who completed the Week 24 Visit in Study 113B or the Week 8 Visit in Study 115.

Approximately 56 subjects from Study 113B and 65 subjects from Study 115 will be enrolled in the study. This study is designed to evaluate the safety and efficacy of long-term TEZ/IVA treatment in subjects who were aged 6 through 11 years at the start of the parent study.

Study 113B and Study 115 were designed to evaluate pharmacokinetics, safety, tolerability, pharmacodynamics, and efficacy to support an expanded indication for TEZ/IVA in subjects 6 through 11 years of age, inclusive, who are homozygous or heterozygous for *F508del*. The long-term safety and efficacy of TEZ/IVA treatment has not yet been evaluated in this age group. Therefore, results from Study 116 will provide information on the safety and efficacy of long-term TEZ/IVA treatment in subjects with CF aged 6 years and older, homozygous or heterozygous for *F508del*.

Interim analyses (IAs), as described in the statistical analysis plan (SAP), may occur at any time during the study (Section 12.3.5.1).

### 9.3.2 Study Drug Dose and Duration

The approved Symdeko dosing regimen for this age group will be used.

#### 9.3.2.1 Subjects ≥12 Years of Age

Subjects who are ≥12 years of age at enrollment, or who turn 12 years of age during the study, will receive a morning dose of TEZ 100 mg/IVA 150 mg (FDC tablet) and an evening dose of IVA 150 mg (tablet).

#### 9.3.2.2 Subjects <12 Years of Age

Subjects who are <12 years of age and weigh <30 kg at the Day 1 Visit will receive a morning dose of TEZ 50 mg/IVA 75 mg (fixed-dose combination [FDC] tablet) and an evening dose of IVA 75 mg (tablet). Subjects who are <12 years of age and ≥30 kg at the Day 1 Visit will receive a morning dose of TEZ 100 mg/IVA 150 mg (FDC tablet) and an evening dose of IVA 150 mg (tablet).If a subject who weighs <30 kg at enrollment subsequently weighs ≥30 kg at 2 consecutive study visits, the study drug dose will be adjusted upward at the second visit such that the subject receives a morning dose of TEZ 100 mg/IVA 150 mg (FDC tablet) and an evening dose of IVA 150 mg (tablet).

### 9.3.3 Rationale for Study Assessments

The safety and efficacy 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.

Ophthalmologic Examinations: A juvenile rat toxicity study performed to support dosing of IVA in subjects <2 years of age demonstrated lens opacities in some animals. Prior studies in rats and dogs of older age did not demonstrate similar findings. Given substantial differences between human and rat lens development, the finding is of unlikely relevance to humans. To confirm this interpretation, periodic ophthalmologic examinations will be performed in this study. The overall data acquired to date do not suggest an association between IVA treatment and cataract development; however, a potential association has not been fully excluded.

LCI Assessment (Subjects From Study 113B LCI Substudy and Study 115 Only): LCI is a measure of ventilation inhomogeneity that is based on tidal breathing techniques which have been evaluated in patients as young as infants.[4, 5] Studies have shown that LCI correlates with

forced expiratory volume in 1 second ($FEV_1$) in its ability to measure airway disease in patients with impacted spirometry assessment, but can also detect lung disease at an earlier stage than spirometry.[6, 7] Furthermore, data from Study VX10-770-106 in CF subjects with an $FEV_1$ >90% showed LCI to be a more sensitive outcome measure than $FEV_1$.

[redacted]

Sweat Chloride: In patients with CF, the underlying CFTR ion transport defect results in elevated sweat electrolyte levels.[8, 9] The sweat chloride test (quantitative pilocarpine iontophoresis) is the most common diagnostic tool for CF. A sweat chloride concentration of ≥60 mmol/L is considered to be diagnostic of CF, whereas <40 mmol/L is considered normal. Based on the mechanisms of action of TEZ and IVA, the sweat chloride test is included in this study as a measure of the effect of TEZ/IVA on CFTR activity.

Nutritional Status (Measured by Weight and BMI): Malnutrition is common in patients with CF because of increased energy expenditures due to lung disease and fat malabsorption. Given that TEZ/IVA is a systemic therapy, it has the potential to improve extrapulmonary manifestations of CF, including those in the gastrointestinal system. Improved nutritional status, defined as an increase in weight and/or BMI, is considered an appropriate endpoint for therapies targeting CFTR and was used in previous clinical studies of CFTR-targeted therapies. To evaluate the effect of TEZ/IVA on growth, change in weight and BMI will be determined.

As children gain weight and height as part of normal growth, adjustment for age and sex is necessary to assess changes in nutritional status. [redacted] Height and weight will be collected at the study visits indicated in the schedule of assessments.

CFQ-R: The CFQ-R is a validated CF-specific instrument that measures the health-related quality of life of patients with CF.[3, 10, 11] The CFQ-R measures quality-of-life domains including respiratory symptoms, digestive symptoms, emotion, and health perception. Furthermore, the CFQ-R has been evaluated in clinical studies involving therapies for CF lung disease.[12-14] Linguistically validated versions of the CFQ-R[15, 16] are available, thereby allowing consistent interpretation of the results in global studies.

[redacted]

[redacted]

## 9.4 Study Restrictions

Study restrictions are summarized in Table 9-1.

Both TEZ and IVA are metabolized predominantly via the hepatic enzymatic pathway utilizing CYP3A4. Co-administration of TEZ and IVA with moderate and strong CYP3A inducers such as rifampin, phenobarbital, carbamazepine, phenytoin, and St. John's wort (*Hypericum perforatum*) has the potential to significantly reduce TEZ and IVA exposure and is restricted in this study. Case-by-case exceptions for concomitant use of a moderate CYP3A inducer with TEZ/IVA may be granted by the Vertex medical monitor if it is the principal investigator's opinion that the benefits outweigh the risks for the subject in question.

A more detailed, but 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**

| Restricted Medication/Food | Study Period |
|---|---|
| Certain fruits and fruit juices (grapefruit, grapefruit juice, Seville oranges, marmalade) | None allowed within 14 days before the first dose of study drug through the Safety Follow-up Visit |
| Moderate and strong CYP3A inducers | None allowed within 14 days before the first dose of study drug through the Safety Follow-up Visit |
| Physician-prescribed or investigational (from another study) IVA [Kalydeco] or lumacaftor/IVA [Orkambi] | None allowed within 30 days before the first dose of study drug through the last dose of study drug |
| Commercially available TEZ/IVA | None allowed within 30 days before the first dose of study drug through the last dose of study drug |

CYP: cytochrome P450, IVA: ivacaftor, TEZ: tezacaftor

## 9.5 Prior and Concomitant Medications

Medicinal products affected by TEZ/IVA (CYP3A, P-glycoprotein, or CYP2C9 substrates)

Co-administration of TEZ/IVA with (oral) midazolam, a sensitive CYP3A substrate, did not affect midazolam exposure. No dose adjustment is required when co-administered with CYP3A substrates.

Based on in vitro data, IVA and its M1 metabolite have the potential to inhibit P-glycoprotein (P-gp). Co-administration of TEZ/IVA with digoxin, a sensitive P-glycoprotein (P-gp) substrate, increased digoxin exposure by 1.3-fold, consistent with weak inhibition of P-gp by IVA. Administration of TEZ/IVA may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. When using concomitant digoxin or other substrates of P-gp with a narrow therapeutic index, TEZ/IVA should be used with caution and appropriate monitoring. IVA may inhibit CYP2C9; therefore, monitoring of the international normalized ratio during co-administration of TEZ/IVA with warfarin is recommended.

Information regarding all prior and concomitant medications, including the subject's CF medications, other medications, and herbal and naturopathic remedies administered at or after completion of treatment in the parent study through the Safety Follow-up Visit, if applicable, will be recorded in each subject's source documents.

- Subjects should remain on a stable CF medication (and supplement) regimen through the Safety Follow-up Visit. 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. Medication changes required for clinical management are allowed during the course of the study and will be recorded in the electronic case report form (eCRF). Restricted/prohibited medication guidelines should still be followed (see Section 9.4 and Table 9-1). Guidelines for stable medication regimens for CF are as follows:
  - Subjects who are taking daily inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
  - Subjects who are on inhaled cycling antibiotics should continue on their prior 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 in the cycle.
  - 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 1 of the inhaled alternating antibiotics.
- There are no restrictions on the concomitant use of corticosteroids.

[redacted]

## 9.6 Administration

On Day 1 through the last dose of study drug (the evening dose administered the day before the Week 96 Visit), study drug tablets will be administered orally as shown in Table 9-2.

At each study visit the TEZ/IVA dose for each subject will be reassessed based on body weight and age and adjusted upward if necessary.

Study drug should be administered within 30 minutes after starting a meal with fat-containing food such as a standard "CF" high-fat, high-calorie meal or snack according to the following guidelines:

**Table 9-2 Study Drug Administration**

| Subjects | Treatment | Time | Drug(s) and Dose(s) Administered |
|---|---|---|---|
| • 6 to 11 years of age and <30 kg at enrollment[a,b] | TEZ 50 mg qd + IVA 75 mg q12h | AM | 1 × TEZ 50-mg/ IVA 75-mg FDC tablet |
| | | PM | 1 × IVA 75-mg tablet |
| • 6 to 11 years of age and ≥30 kg at enrollment[a,b]<br>• 6 to 11 years of age and <30 kg at enrollment who subsequently weighs ≥30 kg during the study[a,b]<br>• ≥12 years of age at enrollment, or subjects who turn 12 years of age during the study | TEZ 100 mg qd + IVA 150 mg q12h | AM | 1 × TEZ 100-mg/ IVA 150-mg FDC tablet |
| | | PM | 1 × IVA 150-mg tablet |

FDC: fixed-dose combination, IVA: ivacaftor, q12h: every 12 hours, qd: daily, TEZ: tezacaftor
Note: Additional details regarding study drug administration for TEZ and IVA will be included in the Pharmacy Manual.
[a] No downward dose adjustments will be made if a subject's weight decreases.
[b] Doses may be adjusted upward as follows: if a subject who is 6 to 11 years of age and weighs <30 kg at enrollment subsequently weighs ≥30 kg at 2 consecutive visits, the study drug dose will be adjusted upward at the second visit such that the subject receives TEZ 100 mg qd/IVA 150 mg q12h.

1. Study drug should be administered q12h (± 2 hours). For each subject, all doses (morning and evening) of study drugs should be administered at approximately the same time each day. For example, if the morning dose of study drug is administered at 08:00 on Day 1, all subsequent morning doses should be administered between 06:00 and 10:00. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. A meal or snack will be provided by the site for the morning dose of study drug.
2. If a subject's scheduled visit is to occur in the afternoon, the following guidelines must be used for administering either the morning or evening dose:
    - 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.

3. For visits after Day 1, subjects will be instructed to bring all used and unused study drug and materials associated with the study drug to the site; study drug will be dispensed at each visit, as appropriate.
4. At the Week 96 Visit, the morning dose of study drug will NOT be administered. The last dose of study drug will be the evening dose administered the day before the Week 96 Visit. Providing a meal or snack during this visit is optional.

## 9.7 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 greater 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.

## 9.8 Dose Modification for Use With Concomitant CYP3A Inhibitors

Dosing recommendations for subjects taking concomitant CYP3A inhibitors are described in Table 9-3. The dosage of TEZ/IVA can be altered only when co-administered with moderate or strong inhibitors of CYP3A. The dosage of TEZ/IVA cannot be otherwise altered, but the investigator can interrupt or stop treatment.

**Table 9-3 Dosing Recommendations for Subjects Taking Concomitant CYP3A Inhibitors**

| Type of Inhibitor | Example of Inhibitor | TEZ/IVA FDC | IVA |
|---|---|---|---|
| Strong CYP3A inhibitor | ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin | 1 tablet twice a week in the morning (3 to 4 days between doses) | No evening dose |
| Moderate CYP3A inhibitor | fluconazole, erythromycin | 1 tablet of TEZ/IVA FDC or 1 tablet of IVA in the morning, taken on alternate days. No evening dose. | |

CYP: cytochrome P450, FDC: fixed-dose combination, IVA: ivacaftor, TEZ: tezacaftor

Note: A more detailed, but nonexhaustive, list of study prohibitions and cautions for food and medication will be provided in the Study Reference Manual.

## 9.9 Discontinuation of Study Participation

If after review of a marketing application, local health authorities decline to approve TEZ/IVA for the treatment of CF in a corresponding population aged ≥12 years, pediatric subjects enrolled in Study 116 with the relevant *CFTR* genotypes may be discontinued after communication to investigators and IRBs/IECs of the risks/benefits related to the safety and efficacy observed for the subset of subjects. In addition, if evaluation of efficacy data from Phase 3 Study VX14-661-110 suggests that the TEZ/IVA treatment does not provide clinically meaningful benefit for a population enrolled in Study 116, Vertex may recommend that subjects with relevant *CFTR* genotypes discontinue the study.

Subjects who become eligible to receive commercially available TEZ/IVA by prescription of a physician may be discontinued from this rollover study at the discretion of the sponsor. The timing of assessments after study discontinuation is described in Section 9.1.2 and Section 9.1.3.

## 9.10 Removal of Subjects

Subjects may withdraw from the study at any time at their own request or at the caregiver's 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 will 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/caregiver. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject/caregiver return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit, if applicable (see Section 9.1.3), and follow up with the subject/caregiver regarding any unresolved AEs.

If the subject/caregiver withdraws consent for the study, no further evaluations should be performed, and no additional data should be collected. Vertex may retain and continue using the study data and samples after the study is over, and may use the samples and information in the development of the study compound, and for other drugs and diagnostics, in publications and presentations, and for education purposes. If the subject withdraws from the study, the study data and samples collected will remain part of the study. A subject/caregiver will not be able to request the withdrawal of his/her information from the study data. A subject/caregiver may request destruction of the samples collected from him/her during the study as long as those samples can be identified as his/her samples.

## 9.11 Replacement of Subjects

Subjects who withdraw or are withdrawn during the study drug Treatment Period 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 Packaging and Labeling

Study drug tablets will be supplied in blister cards by Vertex. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for TEZ and IVA will be included in the Pharmacy Manual.

## 10.3 Study Drug Supply, Storage, and Handling

Blister cards must be stored at room temperature according to Table 10-1 and the instructions provided in the Pharmacy Manual. While at the clinical site, the investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is 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 as described in Section 10.4.

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 | Formulation/Route | Dosage | Storage Condition |
|---|---|---|---|
| TEZ/IVA | FDC; oral | TEZ 50 mg/IVA 75 mg | ≤25°C (77°F) with excursions to 30°C (86°F) |
| | | TEZ 100 mg/IVA 150 mg | ≤25°C (77°F) with excursions to 30°C (86°F) |
| IVA | Tablet, oral | 75 mg or 150 mg | ≤25°C (77°F) with excursions to 30°C (86°F) |

FDC, fixed-dose combination, IVA: ivacaftor, TEZ; tezacaftor

## 10.4 Drug Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of (1) study drug received; (2) study drug dispensed to the subjects/caregivers; and (3) study drug returned by the subjects. Subjects/caregivers will be instructed to return all used and unused materials associated with the study drug 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.

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

The study site staff or pharmacy personnel will retain all materials returned by the subjects/caregivers 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.

## 10.6 Compliance

To ensure treatment compliance, the investigator or designee will supervise all study drug dosing that occurs at the site. At each visit, site personnel will review that the subject is compliant with study drug dosing and remind the subject/caregiver 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 discontinuation of the subject from the study.

## 10.7 Blinding and Unblinding

This will be an open-label study. However, subjects and their parent/caregiver should not be informed of their study-related LCI, [redacted] or sweat chloride results during the study regardless of whether the subject has prematurely discontinued treatment or not.

# 11 ASSESSMENTS

## 11.1 Timing of Assessments

All information regarding the timing assessments is shown in the schedule of assessments (Table 3-1). The following assessments must be performed in the order specified below when more than 1 assessment is required at a particular time point:

1. The CFQ-R must be completed before the start of any other assessments scheduled at that visit.
2. Height and weight measurements should be performed before dosing.
3. ECGs will be performed before dosing and before any other procedures that may affect heart rate (e.g., blood draws).
4. The multiple-breath washout (MBW) assessment (performed for subjects from Study 115 and the Study 113B LCI Substudy only) will be performed [redacted]
5. Both MBW [redacted] will be performed before dosing and should be performed before use of bronchodilators.
6. Blood sampling for clinical laboratory assessments at all visits, except the Day 1 Visit, may be conducted at any time during the visit after the ECG is performed and before the meal or snack.
7. No other assessments should overlap with sweat chloride collection.

## 11.2 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, and weight. Select demographic and baseline characteristic data and medical history will be derived from the parent study. Age, sex, race, and ethnicity will be derived from the parent study, [redacted]

## 11.3 Efficacy

### 11.3.1 Lung Clearance Index (Study 115 and Study 113B LCI Substudy Subjects Only)

LCI derived from $N_2$-MBW testing will be conducted at visits specified in Table 3-1 to evaluate the effect of TEZ/IVA on lung ventilation inhomogeneity. $LCI_{2.5}$ represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value, [redacted]

Pre-bronchodilator MBW testing is defined as MBW testing performed for subjects who have

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

MBW testing should be performed "pre-bronchodilator." MBW testing must be performed before dosing, unless noted otherwise. In the event that a subject forgets to withhold bronchodilator(s), MBW testing should be performed according to the following:

- If a subject's Day 1 MBW testing is pre-bronchodilator, but on a subsequent visit, the subject forgets to withhold bronchodilator use, post-bronchodilator MBW testing will be obtained for that visit only, and the visit will not be rescheduled.
- If on Day 1, the subject forgets to withhold his/her dose of bronchodilator, MBW testing should be performed post-bronchodilator and all subsequent MBW testing (according to the Schedule of Assessments detailed for LCI in Table 3-1) should be performed post-bronchodilator.
- Each MBW test will be recorded in the source documents as pre-bronchodilator or post-bronchodilator.

[redacted] MBW assessments will be performed in multiple replicates. Detailed LCI procedures will be supplied in a separate study manual.

Subjects and their parent/caregiver should not be informed of their study-related LCI results during the Treatment Period.

[redacted]

[redacted]

### 11.3.3 Sweat Chloride

The sweat chloride test is a standard diagnostic tool for CF, serving as a biomarker of CFTR activity. Collection of sweat samples will be performed at visits specified in Table 3-1 using an approved collection device. Sweat samples will be sent to a central laboratory for testing and interpretation of results. Individual sweat chloride test results will not be disclosed to the study sites. Specific instructions for collection, handling, processing, and shipping of sweat chloride samples will be provided in a separate Laboratory Manual.

The sweat chloride test must be conducted before dosing with study drug. At each time point, 2 samples will be collected, 1 sample from each arm (left and right). No other assessments should overlap with collection of sweat chloride.

Subjects and their parent/caregiver should not be informed of their study-related sweat chloride results during the Treatment Period.

### 11.3.4 Weight, Height, and BMI

Weight, height, and BMI (derived) will be assessed. Weight and height will be measured with shoes off and before dosing with study drug at time points noted in Table 3-1.

### 11.3.5 Cystic Fibrosis Questionnaire-Revised

The questionnaire provides information about demographics; general quality of life, school, work, 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 (if applicable).[15, 16]

Subjects will be asked to complete the CFQ-R in their native language. The CFQ-R will be completed before dosing at visits noted in Table 3-1. The CFQ-R should be completed before the start of any assessments scheduled at that visit.

The version and format of CFQ-R will be based on age at baseline, regardless of whether the subject changes age during the study. Parents/caregivers will complete the CFQ-R Parent version on all visits. At the Day 1 Visit of Study 116, all subjects will complete the same version of the CFQ-R that was completed in Study 113B or Study 115. Subjects who are ≥12 years of age after the Day 1 Visit will complete the CFQ-R Child Version themselves, and their parents/caregivers will complete the CFQ-R Parent Version.

[redacted]

[redacted]

## 11.4 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, pulse oximetry, PEs, and ophthalmologic examinations.

### 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 CRF completion guidelines for investigators as well as training will be provided.

### 11.4.2 Clinical Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected as shown in Table 3-1. On Day 1, blood samples will be collected before the first dose of study drug. At all other scheduled visits, these samples will be collected at any time during the visit, but not before the ECG is performed (Section 11.1). Subjects are not required to fast before collection of blood samples; however the meal or snack should be provided after blood collection.

Blood and urine samples will be analyzed at a local or central laboratory. For purposes of study data collection, only laboratory tests done in the central laboratory may be used. Local laboratories may be used at the discretion of the local investigator **only for management of urgent medical issues**. If a local laboratory test value is found to be abnormal and clinically significant, it will 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.

Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1). The safety laboratory test panels are shown in Table 11-1.

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

| Serum Chemistry | Hematology |
|---|---|
| Glucose | Hemoglobin |
| Blood urea nitrogen | Erythrocytes: |
| Creatinine | Mean corpuscular hemoglobin |
| Sodium | Mean corpuscular hemoglobin concentration |
| Potassium | Mean corpuscular volume |
| Calcium | Platelets |
| Chloride | Reticulocytes |
| Magnesium | Leukocytes |
| Bicarbonate | Differential (absolute and percent): |
| Phosphate | Eosinophils |
| Bilirubin, direct bilirubin | Basophils |
| Alkaline phosphatase | Neutrophils |
| Aspartate transaminase | Lymphocytes |
| Alanine transaminase | Monocytes |
| Lactate dehydrogenase | |

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

| | |
|---|---|
| Amylase<br>Lipase<br>Gamma-glutamyl transferase<br>Protein<br>Albumin<br>Creatine kinase | |
| **Vitamin Levels** | |
| Vitamins A, D, E, K, and B12 | |
| **Lipid Panel** | |
| Total cholesterol, triglycerides<br>Low-density lipoprotein (LDL)<br>High-density lipoprotein (HDL) | |

Note: Blood draws do not require fasting, but should occur before the meal or snack.

*CFTR* Genotype:

The *CFTR* genotype result can be taken from Study 113 or Study 115. If the genotype result is not available, subjects will be tested for *CFTR* genotype; if the genotype result from the confirmatory test is exclusionary, then the subject will be removed from the study.

Instructions for collecting a sample for *CFTR* genotyping will be included in the Laboratory Manual.

Pregnancy Testing for Female Subjects of Childbearing Potential Who Are Not Abstinent (Section 11.4.8.1):

Female subjects of childbearing potential must have a negative urine pregnancy test at the Day 1 Visit. Serum pregnancy tests will be conducted at other visits specified in Table 3-1.

If the urine pregnancy test is positive on Day 1, study drug will not be administered and the pregnancy will be confirmed with a serum beta-human chorionic gonadotropin (β-HCG) test. If pregnancy is confirmed, the subject will not be eligible for the study.

For pregnancy tests conducted after dosing, if a serum β-HCG test is positive, the pregnancy will be reported and the subject will be permanently withdrawn from study drug dosing as discussed in Section 11.4.8.2. If a pregnancy test is positive, the procedures outlined in Section 11.4.8.2 will be followed.

Additional Evaluations:

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

### 11.4.3 Liver Function Test Parameters

Liver function testing (alanine transaminase [ALT], aspartate transaminase [AST], gamma-glutamyl transferase [GGT], alkaline phosphatase [ALP], direct bilirubin, and total bilirubin) must be performed as noted in Table 3-1 for serum chemistry while subjects are receiving study drug treatment and at the Safety Follow-up Visit. These blood samples should be processed and shipped immediately per the Laboratory Manual.

Subjects with new treatment-emergent ALT or AST elevations of >3 × upper limit of normal (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 confirmatory 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 (before confirmatory testing), and the medical monitor must be notified, if any of the following criteria is met:

- 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 transaminases is identified, regardless of whether ALT or AST 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 transaminases should have their transaminases monitored closely until levels normalize or return to baseline.

Resumption of Study Drug:

If an alternative, reversible cause of transaminase elevation has been identified, study drug may be resumed once transaminases values decrease to ≤2 × ULN or to baseline levels (as defined in Section 12.3.1). Approval of the medical monitor is required before resumption of study drug. Upon resumption of study drug, transaminases should be assessed weekly for 4 weeks. If a protocol-defined transaminase elevation occurs within 4 weeks of rechallenge with the study drug (with confirmation of the initial elevation by repeat testing within 48 to 72 hours), then the study drug must be permanently discontinued, regardless of the presumed etiology.

### 11.4.4 Physical Examinations and Vital Signs

A PE of all body systems and vital signs assessment will be performed at select study visits (see Table 3-1). At other visits, symptom-directed PEs and symptom-directed vital sign assessments can be performed at the discretion of the investigator or healthcare provider. PEs will also occur at any time during the study if triggered by AEs.

A PE includes a review of the following systems: head/neck/thyroid; eyes, ears, nose, and throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After consenting, any clinically significant abnormal findings in PEs will be reported as AEs.

Vital signs include blood pressure (systolic and diastolic), temperature, pulse rate, and respiration rate. The subject will be instructed to rest for at least 5 minutes before vital signs are assessed.

### 11.4.5 Pulse Oximetry

This 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. This will be assessed following at least a 5-minute rest and before study drug dosing. At visits when study drug is taken at the site, pulse oximetry will be collected before study drug administration.

### 11.4.6 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout according to the Schedule of Assessments (Table 3-1). Additional standard 12-lead ECGs will be performed at any other time, if clinically indicated. The performance of all ECGs will adhere to the following guidelines:

- The subject will be instructed to rest in the supine position for at least 5 minutes before having an ECG performed.
- The ECG will be performed before any other procedures that may affect heart rate, such as blood draws.
- ECGs will be performed in triplicate on Day 1.

Clinically significant ECG abnormalities occurring during the study through the Safety Follow-up Visit will be recorded as AEs.

To ensure safety of the subjects, a qualified individual at the study site will make comparisons to Study 116 Day 1 measurements. If the QTcF is increased by >45 msec from Day 1 or an absolute QTcF value is ≥500 msec for any scheduled ECG, 2 additional ECGs will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>45 msec from Day 1 or ≥500 msec), a single ECG will be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. A subject with a QTcF value above the threshold value will discontinue dosing.

Further details pertaining to ECGs will be provided to sites in the ECG Manual.

### 11.4.7 Ophthalmologic Examination

Ophthalmologic examinations will be performed by a licensed ophthalmologist or optometrist. Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination.

Subjects who did not have an ophthalmologic examination at the end of the parent study will have an ophthalmologic examination at the Day 1 Visit of Study 116 or no more than 28 days after. If a subject had an ophthalmological examination in the parent study less than 28 days before the Day 1 Visit of Study 116, the examination does not need to be repeated on Day 1.

The examination includes:

- measurement of best corrected distance visual acuity of each eye

- pharmacologically dilated examination of the lens with a slit lamp

Subjects will have ophthalmologic examinations as noted in Table 3-1. An ophthalmologic examination will be performed at the Week 48 Visit. Subjects will also have an examination at either the Week 96 Visit (± 28 days) OR the Safety Follow-up Visit, but the examination must be completed by the date of the Safety Follow-up Visit. For subjects who discontinue treatment after receiving at least 1 dose of study drug, this examination may be completed at the ETT Visit or the Safety Follow-up Visit (if applicable [Section 9.1.2]), but must be completed by the date of the Safety Follow-up Visit.

If a cataract or lens opacity is identified and determined to be clinically significant by the ophthalmologist or optometrist within Study 116, the subject/caregiver and Vertex medical monitor will be notified. The subject/caregiver may elect to continue or discontinue study drug treatment. If the subject discontinues study drug treatment, the subject should complete the ETT and the Safety Follow-up Visits (see Sections 9.1.2 and 9.1.3). If the subject continues study drug treatment, more frequent ophthalmologic monitoring should be considered.

### 11.4.8 Contraception and Pregnancy

Standard contraception- and pregnancy-related information and requirements are provided below. It should be noted that some of this information and requirements may have limited applicability in this pediatric population.

#### 11.4.8.1 Contraception

For subjects with an appropriate need for contraception, as determined by their physician, 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.

For female subjects using oral hormonal contraceptives:

1. The oral hormonal contraceptives should be in successful use from at least 60 days before the first dose of study drug (unless otherwise noted) and until 90 days following the last dose of study drug.
2. Female subjects who change their method of contraception to hormonal contraceptive during Study 116 must use a second form of approved contraception for at least 60 days after beginning oral contraceptives.

**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 study drug.

- If the female is of non-childbearing potential, per the following:
  - Documented hysterectomy or a bilateral oophorectomy/salpingo-oophorectomy.
  - 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 at least 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 at least 6 months previously, with a documented 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 as 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 before the first dose of study drug
- Female combined (estrogen and progestogen-containing) or progestogen-only oral hormonal contraception associated with inhibition of ovulation if successfully used for at least 60 days before the first dose of study drug or with a second form of approved contraception for at least 60 days after beginning hormonal contraception.

**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 informed consent signature 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.
- 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.

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

#### 11.4.8.2 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.

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 the medical monitor and Vertex Global Patient Safety (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.

## 12 STATISTICAL AND ANALYTICAL PLANS

### 12.1 Sample Size and Power

This open-label rollover study will enroll subjects from Study 113B and Study 115. No formal sample size calculations have been performed. Approximately 56 subjects from Study 113B and approximately 65 subjects from Study 115 are potentially eligible for enrollment.

### 12.2 Analysis Sets

#### 12.2.1 All Subjects Set

The All Subjects Set will be defined as all subjects who are enrolled in Study 116 or received at least 1 dose of TEZ/IVA in Study 116. This analysis set will be used for all individual subject data listings and the disposition summary table, unless specified otherwise.

#### 12.2.2 Full Analysis Set

The Full Analysis Set (FAS) will be defined as all subjects who are enrolled in Study 116, who received at least 1 dose of TEZ/IVA in Study 116, and have an eligible genotype. The FAS will be used for efficacy analyses, unless otherwise specified.

The 115 FAS will be defined as the subset of FAS who were enrolled in parent Study 115. The 113B FAS will be defined as the subset of FAS who were enrolled in parent Study 113. The 113B LCI FAS will be defined as the subset of Study 113B subjects who had LCI data collected in parent Study 113B.

#### 12.2.3 Safety Set

The Safety Set will be defined as all subjects who are enrolled in Study 116 and who received at least 1 dose of TEZ/IVA in Study 116. The Safety Set will be used for all safety analyses, unless otherwise specified.

### 12.3 Statistical Analysis

The Vertex Biometrics Department or designee will analyze the safety and efficacy data.

The primary objective of this study is long-term safety and tolerability. The secondary objective is long-term efficacy. This section summarizes the statistical analysis of safety and efficacy data. Methodological and related details (e.g., missing data) will be provided in the SAP, which will be finalized before clinical database lock.

The data from Study 116 will be integrated with data from the parent studies for the purpose of safety and efficacy analyses.

**The safety analysis period** is defined as the **treatment-emergent (TE) Period**. The safety analysis period begins at the first dose of study drug in Study 116 and ends 28 days after the last dose of study drug in Study 116, or at the date of Study 116 participation completion, whichever occurs first. Completion of Study 116 participation will be defined in the SAP.

The safety analyses will be performed on the Safety Set over the Safety Analysis Period, unless otherwise specified.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, PEs, ophthalmologic examinations, clinical laboratory values, vital signs, ECG measurements, and pulse oximetry. Only descriptive summaries will be presented and no statistical testing is planned.

**The efficacy analysis period** begins at the first dose of study drug in Study 116 and ends at the last study visit at which efficacy data are collected in Study 116. The efficacy analysis will be performed on all subjects in the FAS by parent study for the efficacy analysis period, unless specified otherwise.

Methods of efficacy analyses will be similar for those used in the parent studies. Each of the secondary endpoints ($LCI_{2.5}$, sweat chloride, CFQ-R, and BMI) will be analyzed using a mixed-effects model for repeated measures (MMRM) with absolute change from baseline during the efficacy analysis period as the dependent variable. The least square (LS) mean and the associated 95% CI at each defined analysis visit will be provided for the corresponding efficacy endpoints.

In addition, descriptive summary statistics will be provided for relevant safety and efficacy parameters.

### 12.3.1 General Considerations

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

All individual subject data for subjects who were enrolled in a parent study and who received at least 1 dose of TEZ/IVA in either parent study or in Study 116 will be presented in individual subject data listings.

**Continuous variables** will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, SE, median, minimum value (min), and maximum value (max).

**Categorical variables** will be summarized using counts and percentages.

**Day 1,** unless specified otherwise, will be defined as the day of the first dose of TEZ/IVA, whether the first dose was taken in the parent study or in Study 116.

**Baseline value**, unless specified otherwise, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of TEZ/IVA, whether the first dose was taken in the parent study or in Study 116. For ECGs, the baseline value will be defined as the average of the last non-missing pretreatment measurements (scheduled or

unscheduled) before the first dose of TEZ/IVA or the average of measurements (triplicate) before the first dose of TEZ/IVA, whether the first dose was taken in the parent study or in Study 116.

**Change (absolute change) from baseline** will be calculated as Post-baseline value − Baseline value.

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

The data from Study 116 will be integrated with data from the parent studies for the purpose of providing robust safety and efficacy analyses.

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

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

**Visit windowing rules:** The analysis visit windows for protocol-defined visits will be provided in the SAP.

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

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

**Multiplicity:** No multiplicity adjustment will be performed.

### 12.3.2 Background Characteristics

#### 12.3.2.1 Subject Disposition

The number of subjects in the following categories will be summarized overall:

- All Subjects Set
- Safety Set
- FAS

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

- Completed treatment
- Prematurely discontinued the treatment and the reason for discontinuation
- Completed study (i.e., completed Safety Follow-up Visit)
- Prematurely discontinued the study and the reason for discontinuation

A listing will be provided for subjects who discontinued study drug treatment or who discontinued the study with reasons for discontinuation.

#### 12.3.2.2 Demographics and Baseline Characteristics

Demographics, medical history, and baseline characteristics will be summarized overall based on the FAS.

Demographic data will include the following:

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

Baseline characteristics will include the following:

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

Disease characteristics will include the following:

- Baseline $LCI_{2.5}$
- Baseline sweat chloride
- Baseline score of CFQ-R respiratory domain

Medical history will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT).

#### 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 (WHO-DDE) and categorized as the following:

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

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

A given medication may be classified as prior, concomitant, or both prior and concomitant.

If a medication has a completely missing or partially missing start/stop date and it cannot be determined whether it was taken before the first dose date or concomitantly, it will be classified as prior and concomitant.

Prior medications and concomitant medications will be summarized descriptively using frequency tables by Preferred Name.

Summaries of medications will be based on the FAS.

Details for imputing missing or partial start and/or stop dates of medication will be provided in the SAP.

#### 12.3.2.4 Study Drug Exposure and Compliance

Duration of study drug exposure (in days) will be calculated as: last dose date – first dose date + 1 day, regardless of study drug interruption.

Exposure summaries will be based on the Safety Set.

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

Study drug compliance based on study drug exposure will be calculated as: 100 × [1 − (total number of days of any study drug interruption) / (duration of study drug exposure in days)].

Study drug compliance will be summarized descriptively by the n, mean, SD, SE, median, min, and max. They will also be summarized in categories: <80% and ≥80% using frequency tables.

Study drug compliance summaries will be based on the FAS.

### 12.3.3 Efficacy Analysis

All efficacy analyses described in this section will be performed by parent study based on the FAS (115 FAS and 113B FAS), unless specified otherwise. LCI analysis will be based on the 115 FAS and the 113B LCI FAS. The analysis will include all available measurements during the efficacy analysis period.

#### 12.3.3.1 Analysis of Primary Efficacy Variables

Not applicable.

#### 12.3.3.2 Analysis of Secondary Efficacy Variables

Methods of efficacy analyses will be similar for those used in the parent studies. Each of the secondary endpoints ($LCI_{2.5}$, sweat chloride, BMI, and CFQ-R) will be analyzed using a MMRM, with absolute change from baseline during the efficacy analysis period as the dependent variable. For subjects from Study 115, only those who were randomized to TEZ/IVA treatment group will be included in the MMRM model.

The model will include the absolute change from baseline as the dependent variable; visit as a fixed effect; and subject as a random effect, with or without adjustment for age, genotype mutation group, and baseline value.

In the model, visit will be treated as a class variable, assuming an unstructured covariance matrix to model the within-subject variability. This model imposes no assumptions on the correlational structure and is considered robust. Denominator degrees of freedom for the *F* test for fixed effects will be estimated using the Kenward-Roger approximation. If there is a convergence problem due to the use of an unstructured covariance matrix, a compound symmetry covariance structure will be used to model the within-subject errors. With a mixed-effects model based on a restricted maximum likelihood estimation used for the primary analysis and assuming that, conditional on fixed and random effects, data are missing at random, no imputation of missing data will be performed.

The LS mean and the associated 95% CI at each defined analysis visit will be provided for the corresponding efficacy endpoints.

[redacted]

### 12.3.4 Safety Analysis

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

- AEs
- Clinical laboratory values (hematology and serum chemistry)
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry
- PE
- Ophthalmologic examination

Safety endpoints will be analyzed based on the Safety Set using data during the Safety analysis period (TE period). Only descriptive summaries will be presented and no statistical testing is planned.

#### 12.3.4.1 Adverse Events

AEs will be classified as pretreatment AEs or treatment-emergent AEs (TEAEs), defined as follows:

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

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

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

Details for imputing missing or partial start dates of AEs are described in the SAP.

AE summary tables will be presented for TEAEs only, overall and by treatment group, and will include the following:

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- TEAEs leading to death

Summaries will be presented by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries.

In addition, a listing containing individual subject AE data for TEAEs leading to treatment discontinuation, serious adverse events (SAEs), and deaths will be provided separately. All AEs, including pretreatment AEs, will be presented in an individual subject data listing.

#### 12.3.4.2 Clinical Laboratory Assessments

For treatment-emergent laboratory measurements, the raw values and change-from-baseline values of the continuous hematology and chemistry results will be summarized in SI units by treatment group and visit.

The number and percentage of subjects with at least 1 laboratory event outside threshold criteria for the event during the TE period will be summarized overall and by treatment group, including a shift of the event from baseline to post-baseline. The threshold criteria will be provided in the SAP.

A listing of subjects with elevated LFT results during the TE period will be presented based on any of the following: AST >3 × ULN, ALT >3 × ULN, GGT >3 × ULN, ALP >3 × ULN, or total bilirubin >2 × ULN. For each subject in the listing, LFT assessments at all time points will be included (scheduled and unscheduled).

Results of the urine/serum pregnancy test will be listed in individual subject data listings only.

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

#### 12.3.4.3 Electrocardiogram

For treatment-emergent ECG measurements, a summary of raw values and change from baseline values will be provided by treatment group and visit for the following standard 12-lead ECG measurements: RR (msec), HR (beats per minute [bpm]), PR (msec), QRS duration (msec), QRS axis (degrees), QT (msec), and QT corrected for HR intervals (QTcF [msec]).

The number and percentage of subjects with at least 1 ECG event outside of the threshold criteria during the TE period will be summarized overall and by treatment group. The threshold value criteria will be provided in the SAP.

#### 12.3.4.4 Vital Signs

For treatment-emergent vital signs measurements, the raw values and change-from-baseline values will be summarized by treatment group and visit: systolic and diastolic blood pressure (mmHg), body temperature (°C), HR (bpm), and respiration rate (breaths per minute).

The number and percentage of subjects with at least 1 event outside the threshold criteria for a vital sign during the TE period will be summarized overall and by treatment group. The threshold value criteria will be provided in the SAP.

#### 12.3.4.5 Physical Examination

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

#### 12.3.4.6 Other Safety Analysis

Not applicable.

### 12.3.5 Interim and IDMC Analyses

#### 12.3.5.1 Interim Analysis

IAs may occur at any time during the study. The timing and IA analysis plans will be documented in the SAP. If a parent study is not completely unblinded during an IA, the analysis will be performed according to the relevant unblinding plan. The details of the unblinding process will be provided in the Unblinding Plan.

#### 12.3.5.2 IDMC Analysis

An IDMC will be formed. The IDMC's objectives and operational details will be defined in a separate document (the IDMC charter). The IDMC will conduct regular planned safety reviews of study data as outlined in the IDMC charter.

Details of the IDMC (Section 9.1.4) analysis will be provided in the IDMC Analysis Plan.

## 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, ECGs, PEs, 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., urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself will be listed as the AE (e.g., bacteria in urine or decreased hemoglobin).

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 is signed until the following time points:

- For subjects who do not enroll: until time of withdrawal of consent
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, 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 9.1.3)
- For enrolled subjects who do not have a Safety Follow-up Visit because they will transition to commercially available CFTR modulator, or if the subject will receive TEZ/IVA through a Vertex-sponsored MAP: through the ETT Visit (Section 9.1.3)

All subjects/caregivers 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. For subjects who consent, but do not subsequently enroll in the study, AEs 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 (Accessed September 2017). 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, 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/caregiver signed the ICF, and the hospitalization or procedure was planned before the subject/caregiver 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 Visit, regardless of causality, will be reported by the investigator to Vertex GPS. In addition, all SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours**.

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]

For questions, 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 (SUSARs) involving the study drug(s) to all regulatory authorities, IECs, 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 data provided to Vertex, 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 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.

For sites participating in the study in the US, and in accordance with the Health Insurance Portability and Accountability Act and associated regulations ("HIPAA") an executed HIPAA authorization shall be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization shall comply with all HIPAA requirements including authorization allowing the site access to and use of the subject's personally identifiable health information, authorization for the site to disclose such information to Vertex, the FDA, and other parties requiring access under the protocol, and statements as to the purpose for which such information may be used and for how long.

### 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.

### 13.2.8 End of Study

The end of study is defined as the last scheduled visit (or contact) of the last subject in the study.

## 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 data captured for the study/SAE Forms for completeness and clarity, 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 data captured for the study/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 CRFs on the subjects for which they are responsible.

A CRF 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 CRF. Source documentation supporting the CRF 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 CRF 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 will provide formal approval of all the information in the CRFs, including any changes made to the CRFs, to endorse the final submitted data for the subjects for whom the investigator is responsible.

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

## 13.6 Publications and Clinical Study Report

### 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 REFERENCES


1 Cystic Fibrosis Foundation. Patient Registry: 2015 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation; 2016.

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3 Quittner AL, Modi A, Cruz I. Systematic review of health-related quality of life measures for children with respiratory conditions. Paediatr Respir Rev. 2008;9(3):220-32.

4 Sinhal S, Galati J, Baldwin DN, Stocks J, Pillow JJ. Reproducibility of multiple breath washout indices in the unsedated preterm neonate. Pediatr Pulmonol. 2010;45(1):62-70.

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6 Gustafsson PM, De Jong PA, Tiddens HA, Lindblad A. Multiple-breath inert gas washout and spirometry versus structural lung disease in cystic fibrosis. Thorax. 2008;63(2):129-34.

7 Lum S, Gustafsson P, Ljungberg H, Hulskamp G, Bush A, Carr SB, et al. Early detection of cystic fibrosis lung disease: multiple-breath washout versus raised volume tests. Thorax. 2007;62(4):341-47.

8 Wilschanski M, Zielenski J, Markiewicz D, Tsui L-C, Corey M, Levison H, et al. Correlation of sweat chloride concentration with classes of the cystic fibrosis transmembrane conductance regulator gene mutations. J Pediatr. 1995;127(5):705-10.

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11 Modi AC, Quittner AL. Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis. J Pediatr Psychol. 2003;28(8):535-45.

12 Vertex Pharmaceuticals Incorporated. Report G241. A Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of VX-770 in subjects with cystic fibrosis and the G551D mutation. Report date: 17 August 2011.

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14 Retsch-Bogart GZ, Quittner AL, Gibson RL, Oermann CM, McCoy KS, Montgomery AB, et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. Chest. 2009;135(5):1223-32.

15 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.

16 Henry B, Aussage P, Grosskopf C, Goehrs JM. Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. Qual Life Res. 2003;12(1):63-76.

[redacted]

# 15 APPENDIX 1: *CFTR* MUTATIONS

Subjects can either be homozygous or heterozygous for the *F508del-CFTR* mutation. Heterozygous subjects must have 1 *F508del* allele and a second eligible residual-function *CFTR* allele or another allele that has been shown to be TEZ/IVA responsive.

The list below represents acceptable mutations for the second *CFTR* allele for heterozygous subjects. Most mutations were evaluated in the TEZ/IVA pivotal Phase 3 studies. However, this is a non-exhaustive list of *CFTR* mutations to be evaluated in this study. Additional mutations may be evaluated and updates to the list of eligible mutations will be communicated to investigative sites through a memorandum. If TEZ/IVA receives marketing approval for additional mutations in any country/region for patients ≥12 years old, a memorandum will be sent to investigative sites in that country/region and the newly approved mutations will also be eligible.

| ***CFTR* Residual-function Mutations** | | | |
|---|---|---|---|
| 2789+5G→A | D110E | D579G | D1152H |
| 3849+10kbC→T | D110H | S945L | D1270N |
| 3272-26A→G | R117C | S977F | E831X |
| 711+3A→G | E193K | F1052V | A1067T |
| E56K | L206W | K1060T | |
| P67L | R352Q | R1070W | |
| R74W | A455E | F1074L | |

# 16 PROTOCOL SIGNATURE PAGES

## 16.1 Sponsor Signature Page

| Protocol #: VX17-661-116 | Version #: 2.3 (US) | Version Date: 08 Nov 2019 |
|---|---|---|
| Study Title: A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Tezacaftor in Combination With Ivacaftor in Subjects With Cystic Fibrosis Aged 6 Years and Older, Homozygous or Heterozygous for the *F508del-CFTR* Mutation | | |

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

[redacted]

## 16.2 Investigator Signature Page

| Protocol #: VX17-661-116 | Version #: 2.3 (US) | Version Date: 08 Nov 2019 |
|---|---|---|
| Study Title: A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Tezacaftor in Combination With Ivacaftor in Subjects With Cystic Fibrosis Aged 6 Years and Older, Homozygous or Heterozygous for the *F508del-CFTR* Mutation | | |

I have read Protocol VX17-661-116, Version 2.3 (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

## 1 TITLE PAGE

*VERTEX PHARMACEUTICALS INCORPORATED*

# Clinical Study Protocol Addendum for Cystic Fibrosis

## Cystic Fibrosis Studies for the Following Programs

[redacted]

**Tezacaftor/Ivacaftor (VX-661/VX-770)**

[redacted]

**Version and Date of Protocol Addendum:** Version 3.0, 29 July 2020
Replaces Version 2.0, dated 15 May 2020

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210-1862, USA

## Summary of Changes to Cystic Fibrosis Clinical Study Protocols

Vertex is currently evaluating several CFTR modulators in clinical studies for the treatment of cystic fibrosis (CF), a serious and life-threatening disease. In completed studies, treatment with these CFTR modulators has generally resulted in rapid, robust, clinically meaningful, and statistically significant improvements in clinical measures, and are generally safe and well tolerated. Adverse events (AEs) seen with these treatments are mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects.

During this COVID-19 pandemic, the safety of the subjects, investigators, and site personnel participating in these clinical studies is Vertex's first priority, thus it is important to minimize any unnecessary risk to COVID-19 exposure through travel to study sites. This addendum summarizes the measures taken for ongoing CF clinical studies. These operational adjustments were implemented to align with Health Authority guidance ensuring the protection of subjects, investigators, and site personnel while maintaining compliance with GCP and minimizing impact to the integrity of the studies. Overall, the benefit-risk of these studies remains favorable.

Vertex recommends that subjects and sites refer to local guidance regarding travel restrictions. There are no operational changes to the study protocols for subjects who can travel to the study sites for their visits. However, to ensure continued safety of subjects who *cannot* travel to the study sites for their visits (for any reason due to COVID-19), specific alternative measures are being implemented to minimize the risk of exposure to COVID-19 (see table below). As the COVID-19 pandemic evolves, Vertex will continue to assess the need for additional actions to ensure the safety of all involved in these clinical studies.

Addendum Version 3.0 summarizes additional measures taken for these ongoing CF clinical studies (see table below) to ensure continued safety.

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Rationale for Change | Study Number |
|---|---|---|
| **Addendum Version 3.0, dated 29 July 2020** | | |
| **Assessments**<br><br>Unscheduled visit(s) will be permissible at the discretion of the investigator(s) or Vertex. The unscheduled visit(s) may be conducted at any time during the study (including after the protocol defined last study visit) in the event assessments specified to be collected at a scheduled visit were not collected due to COVID-19. | To ensure subject safety and/or to facilitate evaluation of safety and/or efficacy if assessments are not performed per the schedule in the protocol due to COVID-19. | [redacted]<br>[redacted]<br>[redacted]<br>VX17-661-116<br>[redacted]<br>[redacted] |
| Implementaion of measures described in addenda versions 1.0 and 2.0, as applicable. | To ensure subject safety and/or to facilitate evaluation of safety and/or efficacy while maintaining study integrity and the safety of subjects and site personnel. | |

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Rationale for Change | Study Number |
|---|---|---|
| **Addendum Version 2.0, dated 15 May 2020** | | |
| **Assessments**<br><br>Weight and height/length/stature may be assessed by subjects or their caregivers using medical grade scales and stadiometers, as indicated per protocol and per local regulation. Sites and subjects will receive training and guidance as needed on these devices.<br><br>Subjects or caregivers will provide these measurements to site personnel by telephone or video call. Investigators will review results and contact subjects for follow-up as needed. All data will continue to be retained in the subject's source files. | To allow for collection of key data to assess safety and/or efficacy while maintaining study integrity and the safety of subjects and site personnel.<br><br>*Addendum 1 allowed for these assessments to be performed by qualified personnel conducting the in-home visits. Addendum 2 allows for these assessments to be performed by subjects or caregivers.* | [redacted]<br>[redacted]<br>[redacted]<br>VX17-661-116<br>[redacted]<br>[redacted]<br>[redacted] |

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Protocol Change | Protocol Change |
|---|---|---|
| **Addendum Version 1.0, dated 24 April 2020** | | |
| **Consenting of Subjects**<br>ICFs may be provided electronically or by post mail to subjects (and/or caregivers, as indicated per protocol). The subjects and/or caregivers will review the ICF with an appropriately qualified member of the investigator's team via telephone contact or video call. After this review, subjects and/or caregivers will consent (or assent, if applicable), and/or reconsent verbally and by signing and dating the ICF and returning it to the site via post mail. The signed and dated ICF will then be signed and dated by the investigator.<br><br>Subjects participating in select studies may have the opportunity to enroll in longterm extension studies. Informed consent (or assent, if applicable), and/or reconsent for subjects (and/or caregivers, as indicated per protocol) may be obtained per the same process described above, as applicable. | To provide alternative methods of obtaining reconsent or consent, as applicable, while ensuring subject safety. | [redacted]<br>VX17-661-116 |
| **Study Drug Shipping**<br>Study drug may be shipped directly from the site to the subject, as applicable, and if permitted by local regulations; subject protected health information will not be released to Vertex.<br><br>Reconciliation, return, and destruction of study drug will continue to occur at the clinical site as indicated per protocol and in adherence to local regulations. | To ensure subjects can continue treatment with study drug without interruption while ensuring their safety.<br><br>To clarify that despite these alternative measures, reconciliation, return, and destruction of study drug will remain as indicated per protocol. | [redacted] |
| **In-home Visits and/or Telephone Contact**<br>Study visits may be conducted as in-home visits by qualified personnel as requested by participating sites on a per-subject basis. In addition, all subjects may be contacted by site personnel by telephone or video call, irrespective of in-home visits. | To provide subjects the opportunity to continue participation in the clinical studies while ensuring their safety by minimizing the risk to COVID-19 exposure through travel. | [redacted] |

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Protocol Change | Protocol Change |
|---|---|---|
| **Addendum Version 1.0, dated 24 April 2020** | | |
| **Safety Assessments and Reporting**<br>Safety assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits (e.g., personnel from site or qualified health care agency). These assessments may include the following, as indicated per protocol, and per local regulation:<br>• vital signs<br>• pulse oximetry<br>• height/length/stature<br>• weight<br>• physical examination (complete or abbreviated)<br>• pregnancy test (serum or urine)<br>• urinalysis<br>• blood draws for safety test panels (chemistry, LFT panel, lipid panel, hematology, coagulation).<br>Blood and/or urine samples for safety assessments are analyzed as indicated per protocol for subjects who have in-home visits.<br>Blood and/or urine samples for safety assessments may be collected and analyzed at local laboratories for subjects who do not have in-home visits, but do not complete the assessment at the site.<br>In addition, safety assessents will be evaluated by telephone. These assessments may include the review of the following:<br>• AEs<br>• signs and symptoms/systems for CF<br>• medications<br>• planned or unplanned hospitalizations for CF<br>• study drug administration<br>• outcomes related to PEx<br>• outcomes related to antibiotic treatment<br>Investigators will review results (in-home and telephone) and contact subjects for follow-up as needed.<br>All data will continue to be retained in the subject's source files.<br>Any clinically significant finding (e.g., AE, SAE, laboratory abnormalities) will continue to be reported as indicated per protocol. | To assess the safety and tolerability of the CFTR modulator evaluated in the specific clinical study while ensuring subject safety. These safety assessments will continue to provide safety data while minimizing burden to subjects and site personnel.<br><br>To clarify that despite these alternative measures, all adverse events and serious adverse events should be reported as indicated per protocol. | [redacted]<br>[redacted]<br>[redacted]<br>VX17-661-116<br>[redacted]<br>[redacted]<br>[redacted]<br>[redacted] |

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Protocol Change | Protocol Change |
|---|---|---|
| **Addendum Version 1.0, dated 24 April 2020** | | |
| **Efficacy and Other Assessments**<br>Efficacy and other assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits. These assessments may include the following, as indicated per protocol, and per local regulation.<br>[redacted]<br><u>Patient Reported Outcome</u><br>CFQ-R questionnaires may be provided to subjects (electronically or post mail) to be completed at home as indicated per protocol. Subjects will return these questionnaires to the site via post mail.<br><u>Other Assessments</u><br>• ECGs<br>• sweat chloride<br>• blood samples for *CFTR* genotype testing, [redacted] PK, FSH, [redacted] and vitamin levels<br>[redacted] | To be able to assess safety, treatment effectiveness, and quality of life measures of the CFTR modulator evaluated in the specific clinical study while ensuring subject safety. | <u>All Efficacy and Other Assessments</u><br>[redacted]<br>VX17-661-116<br>[redacted]<br><u>Other Outcomes Only</u><br>[redacted] |

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Protocol Change | Protocol Change |
|---|---|---|
| **Addendum Version 1.0, dated 24 April 2020** | | |
| **Remote Monitoring**<br>Vertex has implemented remote monitoring visits where applicable, including remote source data verification, as allowed per local regulations. Remote monitoring will focus on collection of safety data, and data supporting primary and key secondary endpoints. | To allow for review of key data to inform on the safety of subjects receiving treatment.<br><br>To allow for review of other key data to inform on the objectives of the study while maintaining study integrity and the safety of subjects and site personnel. | [redacted]<br>[redacted]<br>[redacted]<br>VX17-661-116<br>[redacted]<br>[redacted]<br>[redacted] |

AE: adverse event; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; ECG: electrocardiogram; [redacted] FSH: follicle-stimulating hormone; GCP: Good Clinical Practice; ICF: informed consent form; [redacted] LFT: liver function test; [redacted] PK: pharmacokinetic; SAE: serious adverse event; [redacted]