1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3, Double-blind, Parallel-group Study to Evaluate the Efficacy and Safety of Tezacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, Homozygous or Heterozygous for the *F508del-CFTR* Mutation

Vertex Study Number: VX16-661-115

[redacted]

EudraCT Number: 2016-004479-35

Date of Protocol: 17 November 2017 (Version 1.0)

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

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2 PROTOCOL SYNOPSIS

Title A Phase 3, Double-blind, Parallel-group Study to Evaluate the Efficacy and Safety of Tezacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, Homozygous or Heterozygous for the *F508del-CFTR* Mutation

Brief Title A Study to Evaluate Efficacy and Safety of TEZ/IVA in Subjects Aged 6 through 11 Years With Cystic Fibrosis

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

Objectives

Primary Objective

To evaluate the efficacy of tezacaftor in combination with ivacaftor (TEZ/IVA) in subjects with cystic fibrosis (CF) aged 6 through 11 years, homozygous or heterozygous for *F508del*

Secondary Objective

To evaluate the safety of TEZ/IVA in subjects with CF aged 6 through 11 years, homozygous or heterozygous for *F508del*

Endpoints

Primary Endpoint

Absolute change in lung clearance index$_{2.5}$ ($LCI_{2.5}$) from baseline through Week 8

Secondary Endpoints

- Absolute change from baseline in sweat chloride at Week 8
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline through Week 8
- Safety and tolerability as measured by adverse events (AEs), clinically significant changes in laboratory values (serum chemistry, hematology, coagulation studies, lipids, vitamin levels, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, serial lung function measurement, and ophthalmologic examinations.

[redacted]

Number of Subjects	Approximately 65 subjects total, of which up to 15 subjects are heterozygous for *F508del* and a second *CFTR* allele that results in residual function (F/RF)
Study Population	Male and female subjects aged 6 through 11 years with CF who are F/F or F/RF
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 **Active substance:** Not applicable **Activity:** Placebo **Strength and route of administration:** 0-mg matching placebo tablets for oral administration
Study Duration	Each subject will participate in the study for 16 weeks: 4-week Screening Period, 8-week Treatment Period, and 4-week Safety Follow-up Period.

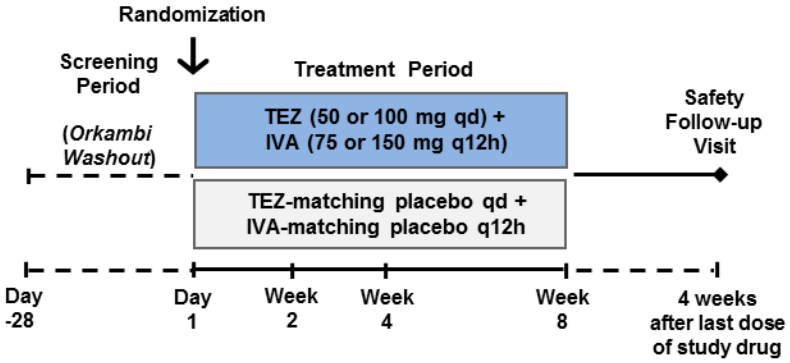
Study Design

This is a Phase 3, double-blind, parallel-group study in subjects with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation. The study is designed to evaluate the efficacy and safety of TEZ/IVA treatment in pediatric subjects aged 6 through 11 years.

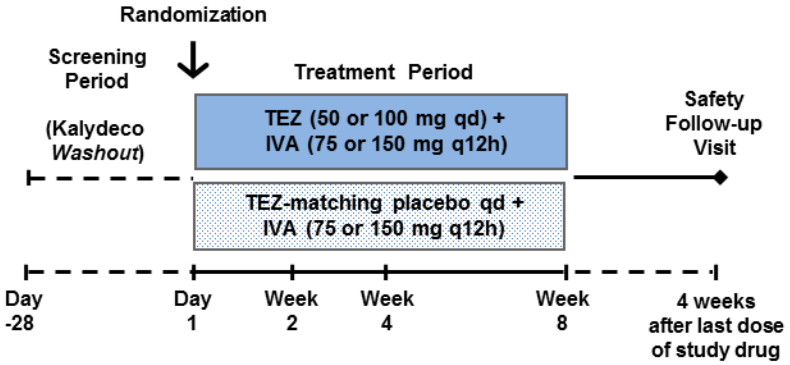
Subjects will be stratified by genotype group (F/F or F/RF) and randomized 4:1 (TEZ/IVA: blinding arm) and treated as shown in Figure 2-1. The blinding arm will be placebo for F/F subjects and IVA monotherapy (with TEZ-matching placebo) for F/RF subjects.

Figure 2-1 VX16-661-115 Study Design

***F/F* Subjects**



***F/RF* Subjects**



Notes: Subjects who are taking commercially available CFTR modulators (Orkambi® or Kalydeco®) are required to washout for 28 days before the Day 1 Visit. Study drug dose is determined based on weight on Day 1 (<40 kg or ≥40 kg). Subjects will receive matched TEZ/IVA placebo or IVA placebo tablets as appropriate. See Table 9-2 for additional information on study drug tablets and dosing.

Subjects will be offered the opportunity to enroll in a 96-week open-label TEZ/IVA extension study (Study VX17-661-116) after completing the Week 8 Visit. The Safety Follow-up Visit is not required for subjects who enroll in the extension study within 4 weeks after the last dose of study drug.

Subjects who prematurely discontinue study drug treatment will be asked to remain in the study and complete the efficacy assessments (LCI, CFQ-R, sweat chloride, [redacted] from the time of discontinuation through the end of the Treatment Period. Subjects who are discontinued due to having an ineligible genotype or due to lack of health authority approval will complete the ETT Visit and are not required to return for additional efficacy assessments because they will be discontinued from the study.

Assessments

Efficacy Assessments

LCI, sweat chloride, CFQ-R [redacted]

Safety Assessments

AEs, clinical laboratory assessments (serum chemistry, hematology, coagulation studies, lipids, vitamin levels, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, spirometry, physical examinations, and ophthalmologic examinations [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 primary objective is to evaluate the efficacy of TEZ/IVA in *F508del* homozygous and heterozygous subjects. The primary efficacy endpoint is the absolute change in $LCI_{2.5}$ from baseline through Week 8.

The objective of the primary efficacy endpoint analysis is to demonstrate that the mean absolute change from baseline in $LCI_{2.5}$ through Week 8 for subjects on TEZ/IVA excludes a pre-defined maximum placebo effect.

The primary analysis of the primary efficacy endpoint will be based on a mixed-effects model for repeated measures with $LCI_{2.5}$ at each time point as the outcome variable. The estimated mean change from baseline through Week 8 in $LCI_{2.5}$ for subjects treated with TEZ/IVA along with the corresponding 95% CI will be provided. If the upper bound of the 95% CI is below the pre-defined maximum placebo effect, it will be interpreted as sufficient evidence to achieve the primary efficacy objective.

Based on Study 809-109 data, -0.10 is used as an estimate for the pre-defined maximum possible effect.

Accounting for a 10% dropout rate, approximately 40 subjects treated with TEZ/IVA will provide at least 90% power to exclude -0.10.

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 Table 3-1.

Table 3-1 Study VX16-661-115: Screening, Treatment Period, Early Termination of Treatment, and Safety Follow-up

		Treatment Period					
Event/Assessment[a]	**Screening Period Day -28 to Day -1**	**Day 1**	**Week 2 (± 3 Days)**	**Week 4 (± 5 Days)**	**Week 8 (± 5 Days)[d]**	**Early Termination of Treatment (ETT) Visit[b]**	**Safety Follow-up Visit (4 Weeks [± 7 Days] After Last Dose of Study Drug)[c]**
Clinic visit	X	X	X	X	X	X	X
Informed consent and assent (if applicable)	X						
CFTR genotype[e]	X						
Inclusion/exclusion criteria review	X	X					
Demographics	X						
Medical history	X						
Medications review	X						
CFQ-R[f]		X	X	X	X	X	X[g]
Height and weight[h]	X	X	X	X	X	X	X

[a] All assessments will be performed before study drug dosing unless noted otherwise (refer to Section 11.1).

[b] If the subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the subject decides to terminate treatment (refer to Section 9.1.4). Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 4 weeks (± 7 days) after their last dose of study drug. If the ETT Visit occurs 3 weeks or later after the last dose of study drug, then the Safety Follow up Visit will replace ETT Visit.

[c] The Safety Follow-up Visit is not required for subjects who enroll in the extension study within 28 days after the last dose of study drug.

[d] Subjects who complete the Week 8 Visit will be offered the opportunity to enroll in Study VX17-661-116, an open-label TEZ/IVA extension study, if they meet the eligibility criteria for the extension study.

[e] All subjects will be tested to assess *CFTR* genotype, regardless of availability of a previous *CFTR* genotype lab report. If the *CFTR* screening genotype result is not received before enrollment, a previous *CFTR* genotype lab report may be used to establish eligibility (Section 8.1).

[f] CFQ-R should be completed before the start of any other assessments.

[g] CFQ-R is only required at the Safety Follow-up Visit for subjects who prematurely discontinue study treatment and do not have the ETT visit.

[h] Height and weight will be measured with shoes off. On Day 1, height and weight will be measured before dosing with study drug. Body Mass Index (BMI) will be derived from assessment of height and weight.

Table 3-1 Study VX16-661-115: Screening, Treatment Period, Early Termination of Treatment, and Safety Follow-up

		Treatment Period					
Event/Assessment[a]	**Screening Period Day -28 to Day -1**	**Day 1**	**Week 2 (± 3 Days)**	**Week 4 (± 5 Days)**	**Week 8 (± 5 Days)[d]**	**Early Termination of Treatment (ETT) Visit[b]**	**Safety Follow-up Visit (4 Weeks [± 7 Days] After Last Dose of Study Drug)[c]**
Vital signs and pulse oximetry[i]	X	X	X	X	X	X	X
Ophthalmologic examination[j]	X					X	X
Physical examination[k]	Full	Abbreviated			Abbreviated		Abbreviated
Standard 12-lead ECG[l]	X	X	X	X	X	X	X
Sweat chloride[m]	X	X			X		X
Pregnancy test (female subjects of childbearing potential)[n]	Serum	Urine		Serum	Serum	Serum	Serum

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

[j] Ophthalmologic examinations will be conducted by a licensed ophthalmologist or optometrist. Ophthalmologic examinations do not need to be completed if there is documentation of bilateral lens removal. The screening examination does not need to be repeated if there is documentation of an examination meeting the protocol requirements that was conducted within 3 months before the date of assent. For additional detail, see Section 11.5.7. For subjects who do not rollover into an extension study, a single end-of-study examination will be done at the ETT or SFUV.

[k] See Section 11.5.4. At other visits, symptom-directed physical examinations will occur if triggered by adverse events or if deemed necessary by the investigator.

[l] All standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes and before any other procedures that may affect heart rate, such as blood draws. During the Treatment Period, ECGs will be performed before dosing. ECGs collected on Day 1 before study drug dosing will be performed in triplicate.

[m] A sweat chloride test must be performed at Screening if an eligible sweat chloride value is not available in the subject's medical records. For subjects using a sweat chloride value documented in their medical record to establish eligibility, the sweat chloride test at the Screening Visit is optional. Collection of sweat chloride will not overlap with any other study assessments. During the Treatment Period, sweat collection will be done approximately at the same time as predose blood collections.

[n] Any female subject who does not meet the criteria for non-childbearing potential (refer to Section 11.5.8.1) is considered to be of childbearing potential and must have pregnancy testing.

Table 3-1 Study VX16-661-115: Screening, Treatment Period, Early Termination of Treatment, and Safety Follow-up

		Treatment Period					
Event/Assessment[a]	**Screening Period Day -28 to Day -1**	**Day 1**	**Week 2 (± 3 Days)**	**Week 4 (± 5 Days)**	**Week 8 (± 5 Days)[d]**	**Early Termination of Treatment (ETT) Visit[b]**	**Safety Follow-up Visit (4 Weeks [± 7 Days] After Last Dose of Study Drug)[c]**
Urinalysis[o]	X	X			X	X	X
Lipid panel[o]		X[p]			X	X	X
Vitamin levels[o]		X[p]			X	X	X
Serum chemistry[o]	X	X[p]	X	X	X	X	X
Hematology[o]	X	X[p]	X		X	X	X
Coagulation studies[o]	X				X	X	X
[redacted]							
Multiple-breath washout (MBW)[s]	X	X	X	X	X		
Spirometry[t]	X	X	X	X	X	X	X
[redacted]							
Meal or snack at clinic		X	X	X	optional		
Study drug count			X	X	X	X	

[o] See Section 11.5.2 for details.

[p] Blood samples to be collected predose on Day 1. At all other scheduled visits, these samples will be collected at any time during the visit.

[redacted]

[s] The MBW assessment will be performed in multiple replicates and before study drug dosing (see Section 11.4.1 and the Study Reference Manual). MBW should be performed pre-bronchodilator and will be performed before the spirometry assessment.

[t] At the Screening Visit, spirometry may be performed pre- or post-bronchodilator. At all visits during the Treatment Period, spirometry must be performed for all subjects before dosing and should be performed pre-bronchodilator. On Day 1 and Week 2, additional spirometry will be performed at 2 (± 30 minutes) and 4 hours (± 30 minutes) postdose. If more than 1 spirometry assessment is required at a visit, bronchodilators should be withheld until the last scheduled spirometry assessment is completed. If study drug is not administered on the day of the visit (i.e., study drug interruption or permanent discontinuation of study drug), the assessment will only be collected once.

[redacted]

Table 3-1 Study VX16-661-115: Screening, Treatment Period, Early Termination of Treatment, and Safety Follow-up

		Treatment Period					
Event/Assessment[a]	**Screening Period Day -28 to Day -1**	**Day 1**	**Week 2 (± 3 Days)**	**Week 4 (± 5 Days)**	**Week 8 (± 5 Days)[d]**	**Early Termination of Treatment (ETT) Visit[b]**	**Safety Follow-up Visit (4 Weeks [± 7 Days] After Last Dose of Study Drug)[c]**
Study drug dosing[v]		X	X	X			
[redacted]							
Concomitant medications, treatments, and procedures	Continuous from signing of informed consent form (and assent form, if applicable) through Safety Follow-up Visit						
Adverse events and serious adverse events	Continuous from signing of informed consent form (and assent form, if applicable) through Safety Follow-up Visit						

[v] The study drug should be administered within 30 minutes after starting a meal with fat-containing food. On days of scheduled visits, the dose of study drug will be administered at the site after predose assessments have been completed. At the Week 8 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 8 Visit. Refer to Section 9.4 for details on study restrictions and Section 9.6 for details on study drug administration.

[redacted]

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List of Abbreviations

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
ATS	American Thoracic Society
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
bpm	beats per minute
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator protein
CI	confidence interval
Cl^-	chloride ion
[redacted]	[redacted]
CRF	case report form
CRO	contract research organization
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
ERS	European Respiratory Society
ETT	Early Termination of Treatment
EU	European Union
F/F	homozygous for *F508del*
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
$FEF_{25\%-75\%}$	forced expiratory flow, midexpiratory phase
FEV_1	forced expiratory volume in 1 second
F/RF	heterozygous for F508del and a second allele with a residual function mutation
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLI	Global Lung Function Initiative
GPS	Global Patient Safety
HIPAA	Health Insurance Portability and Accountability Act and associated regulations
HR	heart rate
ICF	informed consent form

Abbreviation	Term
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	Investigational New Drug (application) (US)
IRB	institutional review board
IV	intravenous
IVA	ivacaftor
IXRS	interactive response system in which X represents voice or web, such as IWRS
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]
LFT	liver function test
LS	least squares
LUM	lumacaftor
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
P	probability
PE	physical examination
PK	pharmacokinetic
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
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
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)
SOC	System Organ Class
SUSAR	suspected, unexpected, serious adverse reaction

Abbreviation	Term
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.[2,3]

Two complementary approaches to increase CFTR-mediated Cl^- secretion in the airway epithelia have been studied.[9] 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 (Kalydeco®; VX-770) were developed by Vertex Pharmaceuticals Incorporated (Vertex). IVA was the first CFTR modulator to show an improvement in CFTR function and clinical benefit in patients with CF and is marketed as Kalydeco. Kalydeco is indicated for the treatment of CF in patients as young as 2 years who have a *G551D,* certain gating, and certain residual function mutations *CFTR*. The indicated mutations and approved populations vary by country. Please refer to local prescribing information for your region for the current approved use of Kalydeco.

Results from 2 pivotal Phase 3 Studies VX14-661-106 (Study 106) and VX14-661-108 (Study 108) evaluating TEZ in combination with IVA (TEZ/IVA) have 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 or heterozygous for *F508del* aged ≥12 years.

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

5.2 Study Rationale

Efficacy, safety, and pharmacokinetics (PK) profiles have been established for TEZ/IVA in subjects with CF who are 12 years of age and older. Preliminary safety and PK profiles for TEZ/IVA have been established in subjects with CF who are 6 through 11 years of age and who are homozygous or heterozygous for the *F508del* in Part A of Study VX15-661-113 (Study 113). Ongoing Study 113 Part B is designed to obtain further PK, safety, tolerability, pharmacodynamics, and efficacy information to support an expanded indication for TEZ/IVA treatment in the pediatric population.

Study 115 is designed to evaluate the efficacy (primary objective) and safety (secondary objective) of TEZ/IVA in subjects aged 6 through 11 years with CF, homozygous or heterozygous for *F508del*.

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the efficacy of TEZ/IVA in subjects with CF aged 6 through 11 years, homozygous or heterozygous for *F508del*

6.2 Secondary Objective

To evaluate the safety of TEZ/IVA in subjects with CF aged 6 through 11 years, homozygous or heterozygous for *F508del*

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Absolute change in lung clearance index$_{2.5}$ (LCI$_{2.5}$) from baseline through Week 8

7.2 Secondary Endpoints

- Absolute change from baseline in sweat chloride at Week 8
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline through Week 8
- Safety and tolerability as measured by adverse events (AEs), clinically significant changes in laboratory values (serum chemistry, hematology, coagulation studies, lipids, vitamin levels, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, serial lung function measurement, and ophthalmologic examinations.

[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 and date 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. Subjects (male and female) will be between the ages of 6 and 11 years, inclusive, on the date(s) of informed consent (and assent, if applicable).
4. Subjects who weigh ≥15 kg without shoes at the Screening Visit.
5. Genotypes as presented in Appendix 1. Genotype is to be confirmed during screening. If the *CFTR* screening genotype result is not received before enrollment, a previous *CFTR* genotype lab report may be used to establish eligibility. Subjects who have been enrolled and whose screening genotype does not confirm study eligibility must be discontinued from the study as described in Section 10.7. Note: Additional mutations may be evaluated and updates to approved mutations will be communicated to investigative sites through a memorandum.
6. A confirmed diagnosis of CF[4] as determined by the following criteria:
   a. **For subjects who are *F508del* homozygous**: confirmed diagnosis of CF defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis (as documented in the subject's medical record OR from the sweat chloride test result obtained at the Screening Visit).
   b. **For subjects who are *F508del* heterozygous:**
      - Confirmed diagnosis of CF defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis (as documented in the subject's medical record [this value may be obtained from a record collected prior to use of

Kalydeco] OR from the sweat chloride test result obtained at the Screening Visit); OR

- If the sweat chloride value is <60 mmol/L, there must be documented evidence of chronic sinopulmonary disease[4] and/or gastrointestinal disease consistent with a diagnosis of CF as judged by the principal investigator, manifest by at least 1 of the following:
    - Persistent colonization/infection, defined as ≥2 positive respiratory cultures within a 6 month period, with 1 or more typical CF pathogens (e.g., *Staphylococcus aureus*, *Haemophilus influenzae*, mucoid and nonmucoid *Pseudomonas aeruginosa*)
    - Chronic cough and sputum production
    - Persistent chest radiograph abnormalities consistent with CF pulmonary disease (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation)
    - Nasal polyps, chronic sinusitis as manifest by radiographic or computed tomographic abnormalities of the paranasal sinuses
    - Evidence of gastrointestinal disease consistent with the diagnosis of CF
    - Significant delays in growth and/or weight gain consistent with the diagnosis of CF

9. Subjects with ppFEV$_1$ of ≥70 percentage points adjusted for age, sex, height, and ethnicity using the Global Lung Function Initiative (GLI) equation[5] at the Screening Visit (Section 11.4.2).
10. Subjects with a screening LCI$_{2.5}$ result ≥7.5.
11. Subjects with stable CF disease as deemed by the investigator at the Screening Visit.
12. Subjects who are willing to remain on their stable CF medication regimen through Week 8 or, if applicable, through the Safety Follow-up Visit.
13. Subjects who are able to swallow tablets.
14. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Day 1 Visit before receiving the first dose of study drug.
15. Subjects of childbearing potential who are sexually active must meet the contraception requirements outlined in Section 11.5.8.1.
16. As deemed by the investigator, the subject's legally appointed and authorized representative (e.g., parent or legal guardian) must be able to understand protocol requirements, restrictions, and instructions. The subject's legally appointed and authorized representative should be able to ensure that the subject will comply with and is likely to complete the study as planned.

8.2 Exclusion Criteria

1. History of any comorbidity reviewed at the Screening Visit 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 Torsades 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, intracranial trauma], and autonomic neuropathy).

2. Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject (as deemed by the investigator).
3. Any of the following abnormal laboratory values at the Screening Visit:
   - Hemoglobin <10 g/dL
   - Abnormal liver function defined as any 2 or more of the following:
     - ≥3 × upper limit of normal (ULN) aspartate aminotransferase (AST)
     - ≥3 × ULN alanine aminotransferase (ALT)
     - ≥3 × ULN gamma-glutamyl transpeptidase (GGT)
     - ≥3 × ULN alkaline phosphatase (ALP)
     - ≥2 × ULN total bilirubin
   - Abnormal liver function defined as any increase of ≥5 × ULN ALT or AST
   - Abnormal renal function defined as glomerular filtration rate ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation)[6]
4. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug).
5. Colonization with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*) at the Screening Visit. The investigator could be guided by the following suggested criteria for a subject to be considered free of colonization:
   - The subject should have had at least 2 respiratory tract cultures negative for these organisms within the past 12 months, with no subsequent positive cultures.
   - These 2 respiratory tract cultures should have been separated by at least 3 months.
   - One of these 2 respiratory tract cultures should have been obtained within the past 6 months.
6. A standard 12-lead ECG demonstrating QTc >450 msec at the Screening Visit. If QTc exceeds 450 msec at the Screening Visit, the ECG should be repeated 2 more times during the Screening Period, and the average of the 3 QTc values should be used to determine the subject's eligibility.
7. History of solid organ or hematological transplantation at the Screening Visit.

8. Ongoing or prior participation in an investigational drug study or use of commercially available CFTR modulator that does not align with the following requirements:
   - A washout period of 30 days or 5 terminal half-lives of the previous investigational study drug, whichever is longer, must elapse before screening.
     - The duration of the elapsed time may be longer if required by local regulations.
   - A washout period of 28 days for investigational lumacaftor/IVA, or physician-prescribed Orkambi® or Kalydeco® must elapse before the Day 1 Visit.

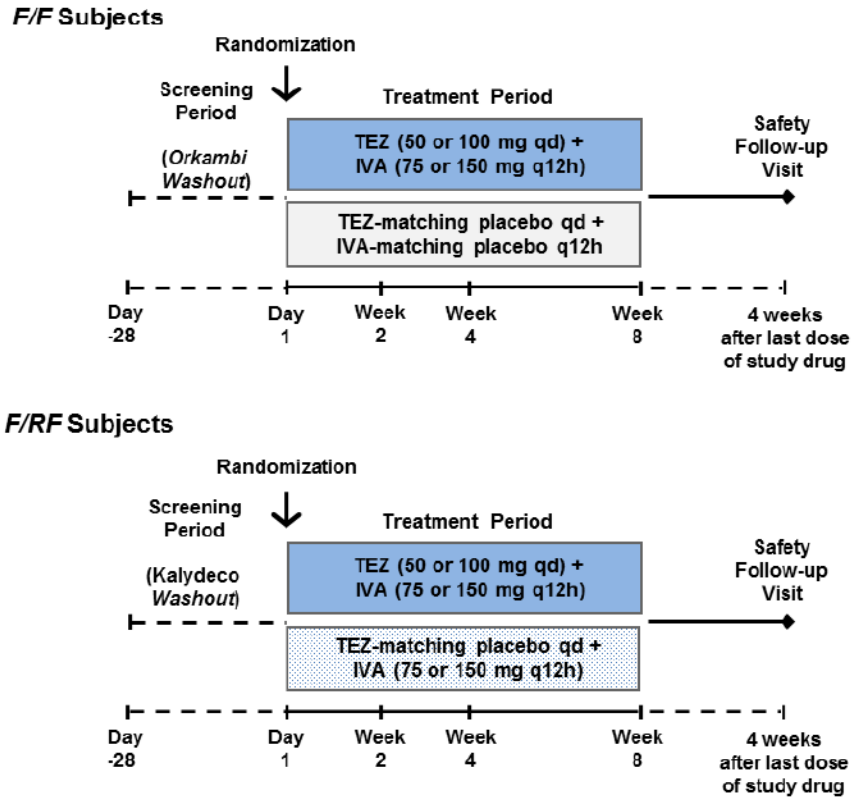
   Note: Ongoing participation in a noninterventional study (including observational studies) is permitted.
9. Use of restricted medication or food within a specified duration before the Screening Visit or first dose of study drug and/or unwillingness to maintain the restrictions as defined in Section 9.4.
10. Pregnant and nursing females.
11. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study.

9 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 3, double-blind, parallel-group study. A schematic of the study design is shown in Figure 9-1.

Figure 9-1 VX16-661-115 Study Design



Notes: Subjects who are taking commercially available CFTR modulators (Orkambi or Kalydeco) are required to washout for 28 days before the Day 1 Visit. The study will enroll a total of approximately 65 subjects, of which up to 15 subjects have an F/RF genotype. Subjects will be stratified by genotype group (F/F or F/RF) and randomized 4:1 (TEZ/IVA: blinding arm) before receiving the first dose of study drug on Day 1. The blinding treatment arm will be placebo for F/F subjects and IVA monotherapy (with TEZ-matching placebo) for F/RF subjects. Study drug dose is determined based on weight on Day 1 (<40 kg or ≥40 kg). Subjects will receive matched TEZ/IVA placebo or IVA placebo tablets as appropriate. See Table 9-2 for additional information on study drug tablets and dosing.

9.1.1 Screening

Screening Visit assessments are listed in Table 3-1.

The Screening Period will occur within 28 days before the first dose of study drug to confirm that subjects meet the selection criteria for the study. To participate in the study, the subject's parent or legal guardian must sign and date a study-specific ICF and the subject must sign an assent form (if applicable) before any study-specific procedures can be performed. The ICF (and assent form, if applicable) will comply with all applicable regulations governing the protection of human subjects and will be approved by Vertex and the site's IRB.

To prepare for study participation, subjects will be instructed on the study restrictions (Section 9.4) and use of concomitant medications (Section 9.5). During the Screening Period, subjects who are being treated with Orkambi or Kalydeco will undergo a 28-day washout before the Day 1 Visit (Table 9-1).

9.1.1.1 Repetition of Screening Period Assessments

Repetition of any individual Screening Visit assessment(s) that does not meet eligibility criteria is not permitted, with the following exceptions:

- If there is clear evidence of a laboratory error (e.g., hemolyzed sample) or equipment malfunction, collection of a repeat sample for the appropriate laboratory test may be permitted after discussion with the Vertex medical monitor or authorized designee.
- If a convincing alternative etiology is identified for elevated transaminases, exclusionary liver function test (LFT) levels may be retested within 14 days of the original Screening Visit date.
- If screening spirometry measurements fail to meet acceptability and repeatability criteria as specified by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines,[7] repeat spirometry evaluation may be performed once.
- If the subject had difficulty completing the multiple-breath washout (MBW) assessment.
- Patients taking physician-prescribed Orkambi or Kalydeco at the Screening Visit can repeat the screening MBW and sweat chloride assessments as needed after approximately 28 days of Orkambi washout.

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

9.1.1.2 Rescreening

Subjects may be rescreened after discussion with, and approval from, the Vertex medical monitor or authorized designee to account for exclusionary events that may not reflect the subject's true baseline due to an acute event, which may resolve.

If a subject is rescreened, all Screening Visit assessments will be repeated except for *CFTR* genotyping, sweat chloride, and the ophthalmologic examination (if the ophthalmologic examination was performed within 3 months before the Rescreening Visit). If a subject is rescreened, the screening window will begin after the first rescreening assessment has been initiated.

9.1.1.3 Extension of Screening Period Window

A subject may have the Screening Period window extended by 2 weeks after approval by the medical monitor or authorized designee for the following reasons:

- Repetition of the Screening Period assessments (Section 9.1.1.1)
- Unexpected operational or logistic delays, or to meet the eligibility criteria
- Scheduling of the ophthalmologic examination (Section 11.5.7)

9.1.2 Treatment Period

Treatment Period assessments are listed in Table 3-1. All subjects will have study visits on Day 1, and Weeks 2, 4, and 8.

The first dose of study drug will be administered on Day 1 and the last dose of study drug will be the evening dose administered the day before the Week 8 Visit. Dosing details are given in Section 9.3.2.

Subjects will be offered the opportunity to enroll in a 96-week open-label TEZ/IVA extension study (Study VX17-661-116) after completing the Week 8 Visit. The Safety Follow-up Visit (Section 9.1.3) is not required for subjects who enroll in the extension study within 4 weeks after the last dose of study drug.

9.1.3 Safety Follow-up

Table 3-1 lists the Safety Follow-up Visit assessments. Subjects will have a Safety Follow-up Visit 4 weeks (± 7 days) after the last dose of study drug. The Safety Follow-up Visit is not required for subjects who have enrolled in the extension study within 28 days after the last dose of study drug.

9.1.4 Early Termination of Treatment

If the subject prematurely discontinues study treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 4 weeks ± 7 days after their last dose of study drug. If the ETT Visit occurs 3 weeks or later after the last dose of study drug, then the Safety Follow-up Visit will replace the ETT Visit and a separate ETT Visit is not required. Subjects who prematurely discontinue treatment will continue to complete all the other scheduled study visits for assessments of efficacy as detailed in the Schedules of Assessments (Table 3-1).

During the course of study conduct, 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 a corresponding adult population, pediatric 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 as soon as possible after the last dose of study drug and a Safety Follow-up Visit should occur approximately 4 weeks ± 7 days after the last dose of study drug. Subjects who are discontinued due to having an ineligible genotype or due to lack of health authority approval (Section 9.8) will complete the ETT Visit and are not required to return for additional efficacy assessments, because they will be discontinued from the study.

If the subject 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 collected before such withdrawal of consent.

9.1.5 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). Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be

included in the IDMC charter. The IDMC charter will be finalized before the first subject is screened.

9.2 Method of Assigning Subjects to Treatment Groups

An interactive web or voice response system (IXRS) will be used to assign subjects to treatment. The randomization code will be produced by Vertex Biostatistics or a qualified randomization vendor. The Vertex study biostatistician will review and approve the production of the final randomization list, which will be reviewed and approved by a designated unblinded biostatistician who is not a member of the study execution team (SET).

9.3 Rationale for Study Design and Study Drug Regimens

9.3.1 Study Design

This is a Phase 3, double-blind, parallel-group study in subjects with CF aged 6 to 11 years, homozygous or heterozygous for *F508del*. Subjects will be:

- homozygous for *F508del* (F/F), or
- heterozygous for *F508del* and a second allele with a residual function mutation (F/RF).

A list of the genotypes eligible for study enrollment is provided in Appendix 1.

Approximately 65 subjects, of which up to15 subjects have an F/RF genotype, will be stratified by genotype and randomized 4:1 to study drug treatment.

Because CF pulmonary disease progresses throughout life, it is not uncommon for patients in the 6- to 11-year age group to have well-preserved or even normal spirometry (e.g., $ppFEV_1$).[8,9] In spite of the potentially normal spirometry, patients in this age group with severe CF-causing mutations already have pulmonary structural aberrations observed through computed tomography scans[9,10] and MBW, which measures the degree of small airway disease by assessing ventilation inhomogeneity. These observations confirm that the disease process that results from lack of CFTR activity begins early in life before spirometry is affected. Because the underlying genetic and molecular etiology of the disease is consistent between this age group and older subjects who have been evaluated in previous TEZ/IVA studies, it is anticipated that TEZ/IVA therapy will be efficacious in this younger population as well.

Efficacy, safety, and PK profiles for TEZ/IVA have been established in subjects ≥12 years of age. Results from 2 pivotal Phase 3 Studies Study 106 and Study 108 have demonstrated clinically meaningful and statistically significant improvements in lung function and key secondary endpoints with TEZ/IVA in CF subjects homozygous or heterozygous for *F508del* aged ≥12 years, along with favorable safety and benefit/risk profiles. Preliminary results from Study 113 Part A show that the exposure, safety, and tolerability of TEZ/IVA are favorable in subjects homozygous or heterozygous for *F508del* who are aged 6 through 11 years.

This study is designed to evaluate the efficacy and safety of TEZ/IVA treatment in a younger pediatric population of CF subjects.

9.3.2 Study Drug Dose and Duration

TEZ/IVA doses were selected based on the exposure, safety, and tolerability results from Study 113 Part A, and results from Study VX11-661-101 which were confirmed in pivotal Phase 3 Studies 106 and 108. All doses are based on subject weight at baseline. The same dose

will be given for the full duration of the study. The dose regimens of IVA (75 mg or 150 mg q12h) are the currently labeled dose regimens for certain populations of patients with CF.

An 8-week Treatment Period duration was selected because significant improvements in lung function were observed after 2 to 4 weeks of treatment with TEZ/IVA and sustained through 24 and 48 weeks of treatment in the pivotal Phase 3 Studies 106 and 108, and during open-label extension Study VX14-661-110 (Study 110), in CF subjects aged ≥12 years.

9.3.2.1 Study Drug Treatment Arms

F/F Subjects Randomized to TEZ/IVA Treatment

Subjects who are <40 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 ≥40 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).

F/F Subjects Randomized to Placebo

Subjects will receive a morning dose of TEZ/IVA-matching placebo (FDC tablet) and an evening dose of IVA-matching placebo (tablet).

F/RF Subjects Randomized to TEZ/IVA Treatment

Subjects who are <40 kg at the Day 1 Visit will receive a morning dose of TEZ 50 mg/IVA 75 mg (FDC tablet), a morning dose of IVA-matching placebo (tablet), and an evening dose of IVA 75 mg (tablet).

Subjects who are ≥40 kg at the Day 1 Visit will receive a morning dose of TEZ 100 mg/IVA 150 mg (FDC tablet), a morning dose of IVA-matching placebo (tablet), and an evening dose of IVA 150 mg (tablet).

F/RF Subjects Randomized to TEZ-matching placebo/IVA Treatment

Subjects who are <40 kg at the Day 1 Visit will receive a morning dose of TEZ/IVA-matching placebo (FDC tablet), a morning dose of IVA 75 mg (tablet), and an evening dose of IVA 75 mg (tablet).

Subjects who are ≥40 kg at the Day 1 Visit will receive a morning dose of TEZ/IVA-matching placebo (FDC tablet), a morning dose of IVA 150 mg (tablet), and an evening dose of IVA 150 mg (tablet).

9.3.3 Rationale for Study Assessments

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

Multiple Breath Washout: LCI, as assessed by multiple breath washout, is a measure of ventilation inhomogeneity that is based on tidal breathing techniques which have been evaluated in patients as young as infants.[11,12] Studies have shown that LCI correlates with 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.[13,14] Furthermore, data from Study VX10-770-106 in CF patients with an FEV_1 >90% showed LCI to be a more sensitive outcome measure than FEV_1.

Spirometry: Since lung disease is the major cause of morbidity and mortality for patients with CF, CF lung disease is the desired primary target of TEZ/IVA combination therapy. Spirometry (as measured by FEV_1) is the most widely implemented standardized assessment to evaluate lung function.

Sweat Chloride: In patients with CF, the underlying CFTR ion transport defect results in elevated sweat electrolyte levels.[15,16] 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.

[redacted]

CFQ-R: The CFQ-R is a validated CF-specific instrument that measures the health-related quality of life of patients with CF.[17,18,19] 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.[20,21,22] Linguistically-validated versions of the CFQ-R[23,24] are available, thereby allowing consistent interpretation of the results in global studies.

[redacted]

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. Periodic ophthalmologic examinations for children aged 11 years and younger receiving IVA are being performed to confirm this interpretation. The overall data acquired to-date does not suggest an association between IVA treatment and cataract development; however, a potential association has not been fully excluded.

[redacted]

9.4 Study Restrictions

Prohibited medications and certain foods are not allowed during the Study Period as summarized in Table 9-1. Both TEZ and IVA are metabolized predominantly via the hepatic enzymatic pathway using CYP3A4. Therefore, the use of known inducers and inhibitors of CYP3A, which have the potential to significantly alter the exposure of TEZ and IVA, will be restricted in this study.

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

Table 9-1 Lifestyle Guidelines and Study Restrictions

	Study Period	
Restricted Medication/Food	**Screening Period**	**Treatment Period**
Certain fruits and fruit juices (grapefruit, grapefruit juice, Seville oranges, marmalade)	None allowed within 14 days before the first dose of study drug	None allowed through the Safety Follow-up Visit
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of study drug	None allowed through the Safety Follow-up Visit
Strong and moderate CYP3A inhibitors (except Ciprofloxacin)	None allowed within 14 days before the first dose of study drug	None allowed through the Safety Follow-up Visit
Investigational or physician-prescribed Orkambi (LUM/IVA) or Kalydeco	None allowed within 28 days before the Day 1 Visit	None allowed through the last dose of study drug
Commercially available TEZ/IVA	None allowed within 28 days before the first dose of study drug	None allowed through the last dose of study drug
Other investigational drugs or devices	None allowed within 30 days or 5 half-lives before screening, or time determined by local requirements; whichever is longer	None allowed through the Safety Follow-up Visit

Note: The use of restricted medication in subjects with a medical need will be addressed on a case-by-case basis with the medical monitor or authorized designee. See the Study Reference Manual for a more complete list of medications prohibited/restricted in the study.

9.5 Prior and Concomitant Medications

Subjects will abstain from all restricted concomitant medications as described in the exclusion criteria (Section 8.2).

Information regarding all prior and concomitant medications, including the subject's CF medications, other medications, and herbal and naturopathic remedies administered from

4 weeks before the Screening Period through the Safety Follow-up Visit will be recorded in each subject's source documents and electronic case report form (eCRF).

- It is recommended that subjects remain on their stable medication regimen for CF from 4 weeks before Day 1 through Week 8 or, if applicable, through the Safety Follow-up Visit. Stable medication regimen is defined as the current medication regimen for CF (except for commercially available CFTR modulators) that subjects have been following for at least 4 weeks before Day 1. Subjects must not initiate long-term treatment with new medication from 28 days before Day 1 through the Safety Follow-up Visit unless discussed and approved by the Vertex medical monitor. 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.
- Subjects may receive doses of prednisone (or prednisolone) of up to 10 mg/day (chronically), or prednisone (or prednisolone) 60 mg qd for up to 5 days with tapering down to 10 mg/day within 2 weeks, without prior approval of the medical monitor.
- Information about bronchodilator use during the study will be collected and documented. Subjects who are using a bronchodilator must have their spirometry assessments performed according to the guidelines provided in Section 11.4.2.
- Concomitant use of medications known to prolong the QT interval should be used with caution during the study, even though the effect of TEZ/IVA on the QT interval has been evaluated in a thorough QT study, which demonstrated no prolongation of the QT interval. Consideration should be given to obtaining an ECG when concomitant medication known to prolong the QT interval is administered.

9.6 Administration

On Day 1 through the evening dose administered the day before the Week 8 Visit (last dose of study drug), study drug tablets will be administered orally as shown in Table 9-2.

Table 9-2 Study Drug Administration

Genotype	Treatment Arm	Subject Weight on Day 1	Time	Drug(s) and Dose(s) Administered; Route of Administration
F/F	TEZ qd/ IVA q12h	<40 kg	AM	1 × TEZ 50-mg/IVA 75-mg FDC tablet; oral
			PM	1 × IVA 75-mg tablet; oral
		≥40 kg	AM	1 × TEZ 100-mg/IVA 150-mg FDC tablet; oral
			PM	1 × 150-mg tablet; oral
	Placebo	<40 or ≥40 kg	AM	1 × TEZ/IVA-matching placebo FDC tablet; oral
			PM	1 × IVA-matching placebo tablet; oral
F/RF	TEZ qd/ IVA q12h	<40 kg	AM	1 × TEZ 50-mg/IVA 75-mg FDC tablet; oral and 1 × IVA-matching placebo tablet; oral
			PM	1 × IVA 75-mg tablet; oral
		≥40 kg	AM	1 × TEZ 100-mg/IVA 150-mg FDC tablet; oral and 1 × IVA-matching placebo tablet; oral
			PM	1 × IVA 150-mg tablet; oral
	TEZ-matching placebo qd/ IVA q12h	<40 kg	AM	1 × TEZ/IVA-matching placebo FDC tablet; oral and 1 × IVA 75-mg tablet; oral
			PM	1 × IVA 75-mg tablet; oral
		≥40 kg	AM	1 × TEZ/IVA-matching placebo FDC tablet; oral and 1 × IVA 150-mg tablet; oral
			PM	1 × IVA 150-mg tablet; oral

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:

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 8 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 8 Visit.

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 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. If a subject has been withdrawn from study drug treatment, the subject 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. 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 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 regarding any unresolved AEs.

If the subject 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 will not be able to request the withdrawal of his/her information from the study data. A subject 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.

9.9 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 to 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 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	Fixed-dose combination tablet; oral	TEZ 50 mg/IVA 75 mg or 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)
TEZ/IVA-matching placebo	Fixed-dose combination tablet; oral	TEZ 0 mg/IVA 0 mg	≤25°C (77°F) with excursions to 30°C (86°F)
IVA-matching placebo	Tablet; oral	IVA 0 mg	≤25°C (77°F) with excursions to 30°C (86°F)

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; and (3) study drug returned by the subjects. Subjects 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 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 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 will contact the medical monitor to discuss discontinuation of the subject from the study.

10.7 Discontinuation of Study Participation

If after review of a marketing application, 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 a corresponding population aged ≥12 years, pediatric subjects enrolled in Study 115, 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 the *CFTR* screening genotype result is not received before enrollment and a previous *CFTR* genotype lab report is used to establish eligibility, enrolled subjects whose screening genotype does not confirm study eligibility must be discontinued from the study and complete an ETT and/or a Safety Follow-up Visit as described in Section 9.1.3 and Section 9.1.4).

10.8 Blinding and Unblinding

This is a double-blind study.

10.8.1 Blinding

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

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the subject and the fetus in the event of a pregnancy
- The unblinded site monitor and unblinded trip report reviewer
- An unblinded pharmacist at the contract research organization (CRO) for dispensing study drug
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy serious adverse event (SAE) processing and reporting regulations
- External vendor (unblinded) statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IXRS Management for IXRS oversight and system administration
- Vertex Clinical Supply Chain
- The bioanalytical CRO laboratory/vendor personnel managed by Vertex Bioanalysis
- The Vertex bioanalytical personnel responsible for reviewing raw data from the bioanalytical CRO, who is not a member of the SET (the Vertex bioanalytical SET member will continue to be blinded).

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

10.8.2 Unblinding

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

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

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

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

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor will be notified within 24 hours of the unblinding event. The reason and the date of the unblinding will be documented clearly in the subject's study file. Information about the treatment assignment obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with the sponsor (Vertex), CRO, or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS or designee, per Section 13.1.2.3.

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

11 ASSESSMENTS

11.1 Timing of Assessments

The 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 should be completed before the start of any other assessments scheduled at that visit.

[redacted]

3. ECGs will be performed before dosing and before any other procedures that may affect heart rate (e.g., blood draws).
4. The MBW assessment should be performed before spirometry.

5. Blood sampling for clinical laboratory assessments at all visits, except the Day 1 Visit, may be conducted at any time during the visit.

[redacted]

The schedule of assessments is shown in Table 3-1.

11.2 Subject and Disease Characteristics

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

[redacted]

11.4 Efficacy

11.4.1 Lung Clearance Index

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

11.4.2 Spirometry

Spirometry will be performed according to the ATS/ERS Guidelines[7] at the time points noted in Table 3-1 according to the additional guidelines that follow.

Pre-bronchodilator spirometry is defined as spirometry 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 spirometry assessment;
- withheld their long-acting bronchodilator (e.g., salmeterol) more than 12 hours before the spirometry assessment; and
- withheld their once-daily, long-acting bronchodilator (e.g., tiotropium bromide [Spiriva]) for more than 24 hours before the spirometry assessment.

All spirometry assessments should be performed "pre-bronchodilator." During the Treatment Period, spirometry assessments must be performed before dosing, unless noted otherwise. In the event that a subject forgets to withhold bronchodilator(s), spirometry should be performed according to the following:

- If a subject's Day 1 spirometry is pre-bronchodilator, but on a subsequent visit, the subject forgets to withhold bronchodilator use, a post-bronchodilator spirometry 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, spirometry should be performed post-bronchodilator and all subsequent spirometric measurements (according to the Schedule of Assessments detailed in Table 3-1) should be performed post-bronchodilator.
- Each spirometry assessment will be recorded in the source documents as pre-bronchodilator or post-bronchodilator.

The parameters listed below will be normalized using the standards of GLI.[5]

- FEV_1 (L)
- Forced vital capacity (FVC) (L)
- FEV_1/FVC (ratio)
- Forced expiratory flow, midexpiratory phase ($FEF_{25\%-75\%}$) (L/s)

All sites will be provided with spirometers and associated materials to be used for all study assessments by the central spirometry service. Spirometry data will be transmitted to a centralized spirometry service for quality review.

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

11.4.3 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 visits during the Treatment Period. At each time point, 2 samples will be collected, 1 sample from each arm (left and right). During the Treatment Period, sweat collection will be done approximately at the same time as predose blood collections.

Collection of sweat chloride will not overlap with any other study assessments.

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

[redacted]

11.4.5 Cystic Fibrosis Questionnaire-Revised

The CFQ-R will be completed at visits noted in Table 3-1. Subjects will be asked to complete the CFQ-R version in their native language if available. Parents/caregivers will complete the CFQ-R parent version each time the subject completes the CFQ-R. The version and format of CFQ-R will be based on age at baseline, regardless of whether the subject changes age during the study. The questionnaires provide information about demographics; general quality of life, school, work, or daily activities; and symptom difficulties (pertaining to CF). Copies of the CFQ-R used in this study will be provided in the Study Reference Manual. Validated translations of the CFQ-R, if available, will be provided for participating centers in non-English-speaking countries (if applicable).[23,24] The CFQ-R should be completed before the start of any assessments scheduled at that visit.

[redacted]

11.5 Safety

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

11.5.1 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.

11.5.2 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.

For purposes of study conduct, only laboratory tests done in the central laboratory may be used. Local laboratories may be used at the discretion of the local investigator 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	Urinalysis[a]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen	Erythrocytes:	Nitrite
Creatinine	Mean corpuscular hemoglobin	Urobilinogen
Sodium	Mean corpuscular hemoglobin concentration	Urine protein
Potassium	Mean corpuscular volume	pH
Calcium	Platelets	Urine blood
Chloride	Reticulocytes	Specific gravity
Magnesium	Leukocytes	Urine ketones
Bicarbonate	Differential (absolute and percent):	Urine bilirubin
Phosphate	Eosinophils	Urine glucose
Bilirubin, direct bilirubin	Basophils	
Alkaline phosphatase	Neutrophils	
Aspartate transaminase	Lymphocytes	
Alanine transaminase	Monocytes	
Lactate dehydrogenase	**Coagulation**	
Amylase	Activated partial thromboplastin time	
Lipase	Prothrombin time	
Gamma-glutamyl transferase	Prothrombin time International Normalized Ratio	
Protein		
Albumin		
Creatine kinase		
Vitamin Levels		
Vitamins A, D, E, K, and B12		
Lipid Panel		
Total cholesterol, triglycerides		
Low-density lipoprotein (LDL)		
High-density lipoprotein (HDL)		

Note: Blood draws do not require fasting.

Pregnancy Testing for Female Subjects of Childbearing Potential Who Are Not Abstinent (Section 11.5.8.1):

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

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 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 11.5.8.2. If a pregnancy test is positive, the procedures outlined in Section 11.5.8.2 will be followed.

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

11.5.3 Liver Function Test Parameters

Liver function testing (ALT, AST, GGT, ALP, direct bilirubin, and total bilirubin) must be performed as noted in Table 11-1 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 × 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. 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.

11.5.4 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 PE and symptom-directed vital sign assessments can be performed at the discretion of the investigator or healthcare provider.

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

The abbreviated PE will include an assessment of the following body systems: head/neck/thyroid, EENT, cardiovascular system, respiratory system, skin, and abdomen.

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.

11.5.5 Pulse Oximetry

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 the morning dose. This is a noninvasive measure of oxygen delivery to the tissues and has been correlated with clinical status and lung function.

11.5.6 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.

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 baseline measurements. If the QTcF is increased by >45 msec from the baseline 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 baseline 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.

11.5.7 Ophthalmologic Examination

Ophthalmologic examinations will be conducted by a licensed ophthalmologist or optometrist according to the schedule in Table 3-1. Subjects with documentation of bilateral lens removal do not need ophthalmologic examinations.

The examination includes:

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

The screening examination does not need to be repeated if there is documentation of an examination meeting the protocol requirements that was conducted within 3 months before the date of assent.

In addition, for subjects who receive at least 1 dose of study drug and do not roll over into an extension study with 28 days of the last dose of study drug in Study 115, a single end-of-study examination will be done at the ETT Visit or 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 115, the subject and Vertex medical monitor will be notified. The subject may elect to continue or discontinue study drug treatment. If the subject discontinues study drug treatment, the subject should complete the ETT and Safety Follow-up Visits (see Sections 9.1.3 and 9.1.4). If the subject continues study drug treatment, more frequent ophthalmologic monitoring should be considered.

11.5.8 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.

11.5.8.1 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.

<u>For female subjects using oral hormonal contraceptives:</u>

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 115 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:

1. 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.
2. 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.

3. If the female is of non-childbearing potential, per the following:
4. Documented hysterectomy or a bilateral oophorectomy/salpingo-oophorectomy.
5. 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.
6. 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 screening must agree to follow the contraceptive requirements of this study if they become sexually active.
- Female condom used with male condom (as a double method of contraception) is not an acceptable method of contraception due to risk of tearing; a different acceptable method of birth control must be used as described in Table 11-2.
- 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.

11.5.8.2 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 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

The sample size of this study is driven by demonstrating that the treatment effect of TEZ/IVA is based on a within-group comparison (change from baseline in $LCI_{2.5}$ in subjects on TEZ/IVA) to exclude a maximum possible placebo effect. If the corresponding 2-sided 95% CI of the change from baseline in $LCI_{2.5}$ in subjects on TEZ/IVA excludes the pre-defined maximum possible placebo effect, it will be considered that the study has achieved its primary objective.

A placebo effect is not expected with LCI, because clinical study data with other Vertex CFTR modulator studies consistently demonstrated a worsening of lung function (i.e., an increase from baseline in LCI) in the absence of CFTR modulator treatment. Study VX14-809-109 (Study 809-109) evaluated treatment with LUM/IVA in F/F subjects aged 6 through 11 years using change from baseline in LCI as the primary efficacy endpoint and provided the most relevant clinical LCI data available in the younger age group of CF subjects. In Study 809-109, the placebo group had a mean worsening in $LCI_{2.5}$ of 0.08 units with an SD of 1.41 (higher numbers indicate a worsening of an LCI measurement); the one-sided 90% lower bound was -0.10 and is used as an estimate for the pre-defined maximum possible placebo effect for Study 115.

Accounting for a 10% dropout rate, approximately 40 subjects on TEZ/IVA will provide at least 90% power to exclude -0.10. The current estimate of the maximum possible placebo effect is based on Study 809-109 placebo data in pediatric F/F subjects with CF. The maximum possible placebo effect is subject to modification before the analysis of Study 115 data is conducted based on the availability of more relevant data; any changes will be documented in the statistical analysis plan (SAP).

12.2 Analysis Sets

12.2.1 All Subjects Set

The All Subjects Set will be defined as all subjects who received at least 1 dose of study drug. 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 were randomized and received at least 1 dose of study drug and had an eligible genotype. The FAS will be used for all efficacy analyses and subjects will be analyzed according to the treatment arm they are randomized to.

12.2.3 Safety Set

The Safety Set will be defined as all subjects who received at least 1 dose of study drug. The Safety Set will be used for all safety analyses, unless otherwise specified. The subjects will be analyzed according to the treatment they received.

12.3 Statistical Analysis

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

The primary objective of this study is efficacy. The secondary objective is safety. This section summarizes the statistical analysis of efficacy and safety data. Methodological and related details (e.g., missing data) will be provided in the SAP.

The primary efficacy endpoint is the absolute change in $LCI_{2.5}$ from baseline through Week 8. The objective of primary efficacy endpoint analysis is to demonstrate that the mean absolute change from baseline in $LCI_{2.5}$ through Week 8 for subjects on TEZ/IVA excludes a pre-defined maximum placebo effect. The primary analysis of the primary efficacy endpoint will be based on a mixed-effects model for repeated measures (MMRM) with $LCI_{2.5}$ at each time point as the outcome variable. The estimated mean change from baseline through Week 8 in $LCI_{2.5}$ for subjects on TEZ/IVA along with the corresponding 95% CI will be provided. If the upper bound of the 95% CI is below the pre-defined maximum possible placebo effect, it will be interpreted as sufficient evidence to achieve the primary efficacy objective.

The study plans to enroll approximately 50 F/F subjects and up to 15 F/RF subjects.

A placebo group of F/F subjects and an IVA mono group of F/RF subjects will be included in this study. The main purpose is to preserve blinding, so that subjects and investigators do not assume a subject is receiving TEZ/IVA, which could introduce bias into the results. Descriptive statistics such as mean and SD will be provided for change from baseline in $LCI_{2.5}$ at each post-baseline visit for homozygous subjects in the placebo group.

The target enrollment by genotype and treatment group is provided in the Table 12-1.

Table 12-1 Target Enrollment by Genotype and Study Drug Treatment

Genotype	N	Study Drug Treatment
F/F	40	TEZ (50 or 100 mg qd) + IVA (75 or 150 mg q12h)
	10	TEZ-matching placebo (qd) + IVA-matching placebo (q12h)
F/RF	12	TEZ (50 or 100 mg qd) + IVA (75 or 150 mg q12h)
	3	TEZ-matching placebo (qd) + IVA (75 or 150 mg q12h)

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 randomized or received at least 1 dose of study drug 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.

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

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.

Treatment-emergent (TE) Period will include the time from the first dose to the earliest of the following: the Safety Follow-up Visit, or 28 days after the last dose of the study drug for subjects who do not have a Safety Follow-up Visit. The TE period will be used for safety analyses unless specified otherwise.

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 for hypothesis testing.

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
- Enrolled in a rollover extension study

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 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 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 based on the FAS, unless specified otherwise. The analysis will include all available measurements through the last scheduled on-treatment visit, including measurements after treatment discontinuation.

12.3.3.1 Analysis of Primary Variables

The objective of primary efficacy endpoint analysis is to demonstrate that the mean absolute change from baseline in $LCI_{2.5}$ through Week 8 excludes a pre-defined maximum placebo effect in subjects in the TEZ/IVA group. The primary analysis for the primary efficacy endpoint will be based on an MMRM using SAS PROC MIXED for the subjects in the TEZ/IVA treatment group in the FAS population. The MMRM will be used to estimate the within-group mean absolute change in $LCI_{2.5}$ through Week 8 in the TEZ/IVA treatment group. The estimated mean change from baseline through Week 8 in $LCI_{2.5}$ for subjects on TEZ/IVA along with the corresponding 95% CI will be provided. If the upper bound of the 95% CI is below the pre-defined maximum possible placebo effect, it will be interpreted as sufficient evidence to reject the null hypothesis.

The model will include absolute change from baseline in $LCI_{2.5}$ (including all measurements up to Week 8 [inclusive], both on treatment measurements and measurements after treatment discontinuation) as the dependent variable, and visit (as a class variable) as a fixed effect, with adjustment for mutation group based on the second *CFTR* allele (F/F and F/RF) and baseline $LCI_{2.5}$ value as fixed effects, and subject as a random effect. An unconstructed covariance structure will be used to model the within-subject errors.

Summary statistics (mean and SD) for change from baseline in $LCI_{2.5}$ through Week 8, and at each visit will also be provided for subjects in the TEZ/IVA treatment group overall.

For homozygous subjects in the placebo treatment group, summary statistics (mean and SD) will be provided for change from baseline in $LCI_{2.5}$ through Week 8, and at each visit.

12.3.3.2 Analysis of Secondary Efficacy Variables

A model similar to the MMRM for the primary analysis of the primary efficacy endpoint will be used with the addition of baseline sweat chloride as a covariate for subjects in the TEZ/IVA treatment group. Average absolute change from baseline in sweat chloride through Week 8 and absolute change from baseline in sweat chloride at each post baseline visit, including least squares (LS) means, SE, and the 2-sided 95% CI along with the *P* value will be provided based on the FAS.

Analysis of absolute change in CFQ-R respiratory score from baseline though Week 8 will be performed using the same model as described for the primary analysis of the primary efficacy endpoint, with the addition of baseline CFQ-R respiratory score as a covariate.

[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
- Physical examination
- Ophthalmologic examination
- Serial lung function

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 date of study drug

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

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, 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, including coagulation studies 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.

For each LFT laboratory test (ALT, AST, ALP, GGT, and total bilirubin), a scatter plot of the maximum treatment-emergent value versus the baseline value corresponding to #× ULN will be presented. Further, a scatter plot of the maximum treatment-emergent value of ALT and AST,

separately, versus the maximum treatment-emergent value of total bilirubin corresponding to × ULN will also be presented.

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

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

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 (mm Hg), 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

12.3.4.6.1 Serial Lung Function

For the 2-hour and 4-hour postdose spirometry measurements on Day 1 and Week 2, a summary of raw values for $ppFEV_1$ will be provided at each time point. The absolute change from the predose value of $ppFEV_1$ on the same day will be summarized at each time point.

12.3.5 Interim and IDMC Analyses

12.3.5.1 Interim Analysis

Not applicable.

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 9.1.5) 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 screen failure (e.g., screen failure, 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 9.1.4)

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

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

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed 10 November 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. "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 signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure will not be considered to

indicate an SAE, unless an AE caused the hospitalization or procedure to be rescheduled sooner or to be prolonged relative to what was planned. In addition, hospitalizations clearly not associated with an AE (e.g., social hospitalization for purposes of respite care) will not be considered to indicate an SAE.

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

13.1.2.2 Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through the Safety Follow-up 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]

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

[redacted]

13.6.2 Clinical Study Report

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

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[redacted]

15 APPENDIX 1: *CFTR* MUTATIONS

Subjects can either be homozygous or heterozygous for the *F508del* mutation. Heterozygous subjects must have *F508del* on 1 allele and a second eligible *CFTR* allele. 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 approved mutations will be communicated to investigative sites through a memorandum.

***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	

During the course of study conduct, 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 a corresponding population aged ≥12 years, pediatric subjects enrolled in Study 115 with the relevant *CFTR* genotypes may not be enrolled into the study. Subjects who are enrolled in Study 115 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.

16 PROTOCOL SIGNATURE PAGES

16.1 Sponsor Signature Page

Protocol #: VX16-661-115	Version #: 1.0	Version Date: 17 November 2017
Study Title: A Phase 3, Double-blind, Parallel-group Study to Evaluate the Efficacy and Safety of Tezacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, 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 #: VX16-661-115	Version #: 1.0	Version Date: 17 November 2017
Study Title: A Phase 3, Double-blind, Parallel-group Study to Evaluate the Efficacy and Safety of Tezacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, Homozygous or Heterozygous for the *F508del-CFTR* Mutation		

I have read Protocol VX16-661-115, Version 1.0, and agree to conduct the study according to its terms. I understand that all information concerning IVA and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date