

1 TITLE PAGE



*VERTEX PHARMACEUTICALS INCORPORATED*

## **Clinical Study Protocol**

**A Phase 3, Randomized, Double-blind, Controlled  
Study Evaluating the Efficacy and Safety of VX-659  
Combination Therapy in Subjects With Cystic  
Fibrosis Who Are Heterozygous for the *F508del*  
Mutation and a Minimal Function Mutation (F/MF)**

**Vertex Study Number: VX17-659-102**

**EudraCT Number: 2017-004132-11**

**Date of Protocol: 27 April 2018 (Version 3.0)**

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## 2 PROTOCOL SYNOPSIS

**Title** A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-659 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the *F508del* Mutation and a Minimal Function Mutation (F/MF)

**Brief Title** A Phase 3 Study of VX-659 Combination Therapy in Subjects With Cystic Fibrosis Heterozygous for the *F508del* Mutation and a Minimal Function Mutation (F/MF)

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

**Objectives Primary Objective**

To evaluate the efficacy of VX-659 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects with cystic fibrosis (CF) who are heterozygous for *F508del* and a minimal function mutation (F/MF subjects)

**Secondary Objectives**

- To evaluate the safety of VX-659 in TC with TEZ and IVA
- To evaluate the pharmacodynamics (PD) of VX-659 in TC with TEZ and IVA
- To evaluate the pharmacokinetics (PK) of VX-659, TEZ, and IVA when administered in TC

**Endpoints Primary Endpoint**

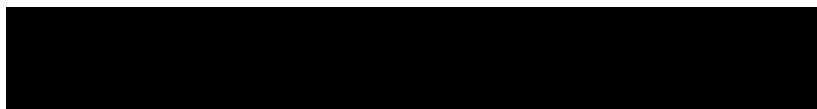
Absolute change in percent predicted forced expiratory volume in 1 second (ppFEV<sub>1</sub>) from baseline at Week 4

**Key Secondary Endpoints**

- Absolute change in ppFEV<sub>1</sub> from baseline through Week 24
- Number of pulmonary exacerbations (PEX) through Week 24
- Absolute change in sweat chloride (SwCl) from baseline through Week 24
- Absolute change in CF Questionnaire-Revised (CFQ-R) respiratory domain score from baseline through Week 24
- Absolute change in body mass index (BMI) from baseline at Week 24
- Absolute change in SwCl from baseline at Week 4
- Absolute change in CFQ-R respiratory domain score from baseline at Week 4

**Other Secondary Endpoints**

- Time-to-first PEX through Week 24
- Absolute change in BMI z-score from baseline at Week 24
- Absolute change in body weight from baseline at Week 24
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry
- PK parameters of VX-659, TEZ, M1-TEZ, and IVA



**Number of Subjects** Approximately 360 subjects will be randomized (1:1) to the TC VX-659/TEZ/IVA arm or the triple placebo arm.

**Study Population** Male and female subjects with CF who are 12 years of age or older and heterozygous for the *F508del* mutation and an MF mutation (F/MF subjects)

**Investigational Drug** Study drug refers to VX-659/TEZ/IVA, IVA, and their matching placebos. Active study drugs will be orally administered as 2 fixed-dose combination (FDC) film-coated tablets (VX-659/TEZ/IVA) in the morning and as 1 film-coated IVA tablet in the evening.

**Active substance:** VX-659, TEZ (tezacaftor; VX-661), and IVA (ivacaftor; VX-770)

**Activity:** CFTR corrector, CFTR corrector, and CFTR potentiator (increased Cl<sup>-</sup> secretion)

**Strength:** 120 mg/50 mg/75 mg

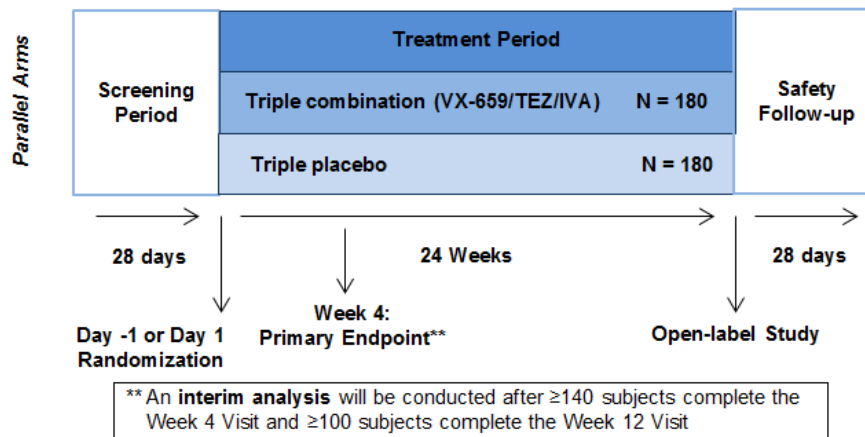
**Active substance:** IVA (ivacaftor; VX-770)

**Activity:** CFTR potentiator (increased Cl<sup>-</sup> secretion)

**Strength:** 150 mg

**Study Duration** The total study duration is approximately 32 weeks (4 weeks for the Screening Period, 24 weeks for the Treatment Period, and 4 weeks for the Safety Follow-up Period).

**Study Design** This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study.



IVA: ivacaftor; N: number of subjects; TEZ: tezacaftor

Notes: The figure is not drawn to scale.

Approximately 360 subjects will be randomized (1:1) to the TC arm or triple placebo arm. The dosages to be evaluated are shown in the table below. Randomization will be stratified by ppFEV<sub>1</sub> determined during the Screening Period (<70 versus ≥70), age at the Screening Visit (<18 versus ≥18 years of age), and sex (male versus female).



**Treatment Arms and Dosages**

Treatment Arm	VX-659 Dosage	TEZ Dosage	IVA Dosage
TC	240 mg qd	100 mg qd	150 mg q12h
Triple placebo	0 mg	0 mg	0 mg

IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TC: triple combination; TEZ: tezacaftor

**Assessments** **Efficacy:** Spirometry, documentation of events related to health outcomes (e.g., PEx), CFQ-R, height (for subjects  $\leq 21$  years of age only), and weight

**PD:** SwCl

**Safety:** AEs, clinical laboratory assessments, ECGs, vital signs, pulse oximetry, physical examinations, and ophthalmologic examinations (for subjects  $< 18$  years of age)

**PK:** VX-659, TEZ, M1-TEZ, and IVA plasma concentrations

**Statistical Analyses** The primary efficacy endpoint is the absolute change in ppFEV<sub>1</sub> from baseline at Week 4. The primary null hypothesis to be tested is that the mean absolute change in ppFEV<sub>1</sub> from baseline is the same for the 2 treatment groups, VX-659/TEZ/IVA and placebo. The null hypothesis will be tested at an overall 2-sided significance level of 0.05.

An interim analysis (IA) is planned when at least 140 subjects complete the Week 4 Visit and at least 100 subjects complete the Week 12 Visit. The IA will be performed by an external independent biostatistician who is not involved in and will not influence the conduct of the study, and the results will be reviewed by an independent data monitoring committee (IDMC). A Lan and DeMets alpha spending function will be applied to control the overall type I error rate of 0.05 for the primary endpoints during the IA and the final analysis such that an alpha of 0.01 will be preserved for the final analysis. If the number of subjects included in the IA is 140, then the primary endpoint of the absolute change from baseline in ppFEV<sub>1</sub> at Week 4 will be tested at a significance level of 0.044 during the IA. The actual alpha at the IA ( $\alpha_0$ ) will be determined based on the actual number of subjects included in the IA. Assuming a within-group SD of 7 percentage points and a 5% dropout rate at Week 4, an IA sample size of 70 subjects in each treatment group will have approximately 98% power to detect a difference between the treatment groups of 5.0 percentage points for the mean absolute change in ppFEV<sub>1</sub> from baseline at Week 4, based on a 2-sided, 2-sample *t*-test at a significance level of 0.044.

If the *P* value for the primary endpoint at the IA is less than  $\alpha_0$ , then the efficacy boundary has been crossed. If the IDMC declares that the study has crossed the efficacy boundary, then the study may be unblinded to a limited Vertex team to prepare regulatory submission(s). Members of the limited Vertex unblinded team will not be involved in or influence the conduct of the remaining part of the study to protect the integrity of the study.

If the *P* value fails to cross the efficacy boundary during the IA, then the primary endpoint of absolute change in ppFEV<sub>1</sub> from baseline at Week 4 will be tested after all subjects complete study participation at an alpha of 0.01. Assuming a within-group SD of 7 percentage points and a 5% dropout rate at Week 4 and 10% dropout rate at Week 24, a final analysis sample size of 180 subjects in each treatment group will have approximately 99% power to detect a difference between the treatment groups of 5.0 percentage points for the mean absolute change in ppFEV<sub>1</sub> from baseline at Week 4, based on a 2-sided, 2-sample *t*-test at a significance level of 0.01.

The analysis of the primary endpoint during the IA will be based on a mixed-effects model for repeated measures (MMRM) with the absolute change from baseline in ppFEV<sub>1</sub> at Day 15 and Week 4 as the dependent variable. During the final analysis, the same model will be implemented, including all available data. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects; with sex (male versus female), continuous baseline ppFEV<sub>1</sub>, and age at screening (<18 versus ≥18 years of age) as covariates; and with an unstructured covariance structure for the within-subject errors.

The primary result obtained from the model will be the estimated treatment difference at Week 4. The adjusted mean difference at Week 4 with 2-sided 95% confidence intervals and 2-sided *P* values will be provided. Furthermore, the adjusted mean and treatment difference at each post-baseline visit, obtained from the model at the final analysis, will also be provided.

The key secondary endpoints will be formally tested only during the final analysis when all subjects complete study participation, at the significance level of 0.05, if the primary endpoint is statistically significant at either the IA or at the final analysis.

The safety endpoints include AEs, clinical laboratory values, ECGs, vital signs, and pulse oximetry through the Safety Follow-up Visit. The safety analysis will be descriptive only.

**IDMC Reviews** An IDMC will conduct periodic planned safety review(s) of study data and the planned efficacy IA, as outlined in the IDMC charter.



### 3 SCHEDULE OF ASSESSMENTS

Table 3-1 and Table 3-2 provide the schedule of assessments during the study.

All visits will be scheduled relative to the Day 1 Visit (first dose of VX-659/TEZ/IVA or matched placebo).

The Cystic Fibrosis Questionnaire–Revised (CFQ-R), [REDACTED] must be completed before any other assessment at relevant clinic visits. Remaining assessments may be performed in any order when more than 1 assessment is required at a particular time point. All assessments will be performed before study drug dosing (Section 9.6.1), unless noted otherwise.



**Table 3-1 Study VX17-659-102: Screening**

Event/Assessment	Screening Period (Day -28 Through Day -1)
ICF and assent (when applicable)	X
Inclusion and exclusion criteria review	X
Demographics	X
Medical history	X
CFQ-R <sup>a</sup>	X
<i>CFTR</i> genotype <sup>b</sup>	X
G6PD activity test	X
FSH <sup>c</sup>	X
Serum pregnancy test (all females of childbearing potential) <sup>d</sup>	X
Hematology	X
Coagulation	X
Serum chemistry	X
Urinalysis	X
Weight and height <sup>e</sup>	X
Ophthalmologic examination <sup>f</sup>	X
Complete physical examination	X
Vital signs <sup>g</sup>	X
Pulse oximetry <sup>g</sup>	X
Standard 12-lead ECG <sup>h</sup>	X
Spirometry <sup>i</sup>	X
Medications review <sup>j</sup>	X
Sweat chloride	X
AEs and SAEs	Continuous from signing of the ICF through completion of study participation

AE: adverse events; CFQ-R: CF Questionnaire-Revised; FSH: follicle-stimulating hormone; G6PD: glucose-6-phosphate dehydrogenase; ICF: informed consent form; SAE: serious adverse event

<sup>a</sup> The CFQ-R must be completed before the start of any other assessments scheduled for that visit.

<sup>b</sup> *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility. Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).

<sup>c</sup> FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be in the postmenopausal range, as determined by the laboratory performing the test, to be considered postmenopausal.

<sup>d</sup> Any female subject who does not meet the criteria for non-childbearing potential is considered to be of childbearing potential and must have a serum pregnancy test. A definition of non-childbearing potential is provided in Section 11.7.7.1.

<sup>e</sup> Weight and height will be measured with shoes off.

<sup>f</sup> Ophthalmologic examinations will be conducted only for subjects who are <18 years of age on the date of informed consent. For subjects with documentation of bilateral lens removal, ophthalmologic examinations are not required. The ophthalmologic examination does not need to be conducted if there is documentation of an examination meeting the protocol requirements that was conducted within 3 months before the date of informed consent (Section 11.7.6). The ophthalmologic examination will be conducted by a licensed ophthalmologist or optometrist.

<sup>g</sup> Vital signs and pulse oximetry will be collected after the subject has been at rest for at least 5 minutes.

<sup>h</sup> A standard 12-lead ECG will be performed after the subject has been at rest for at least 5 minutes.

<sup>i</sup> Spirometry may be performed pre- or post-bronchodilator (Section 11.6.1).

<sup>j</sup> Refer to Section 9.5 for details.

**Table 3-2 Study VX17-659-102: Treatment Period and Safety Follow-up Visit**

Event/Assessment <sup>a</sup>	Day 1	Day 15 (± 3 Days)	Week 4 (± 5 Days)	Week 8 (± 5 Days)	Week 12 (± 5 Days)	Week 16 (± 5 Days)	Week 20 (± 5 Days)	Week 24 (± 5 Days)	ETT Visit <sup>b</sup>	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug (If Applicable) <sup>c</sup>
Clinic visit	X	X	X	X	X	X		X	X	X
Telephone contact							X <sup>d</sup>			
Inclusion and exclusion criteria confirmation	X									
CFQ-R <sup>e</sup>	X		X	X	X	X		X	X	X
Weight and height <sup>f</sup>	X	X	X	X	X	X		X	X	X
Ophthalmologic examination								X <sup>g</sup>	X <sup>g</sup>	X <sup>g</sup>

<sup>a</sup> All assessments will be performed before dosing unless noted otherwise.

<sup>b</sup> If the subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the decision to discontinue treatment. Subjects who prematurely discontinue treatment will continue to complete all scheduled study visits for assessments following completion of the ETT Visit (Section 9.1.4).

<sup>c</sup> The Safety Follow-Up Visit is required for all subjects, unless the subject completes the Week 24 Visit and has enrolled in a separate open-label study within 28 days after the last dose of study drug (Section 9.1.3). If an ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit replaces the Safety Follow-up Visit (Section 9.1.4).

<sup>d</sup> Telephone contact will be made to assess the subject’s status, any AEs, concomitant medications, treatments, and procedures.

<sup>e</sup> The CFQ-R, [REDACTED] must be completed before any other assessments scheduled at relevant visits. Refer to Section 11.6.3 and [REDACTED]

<sup>f</sup> Weight and height will be measured with shoes off. Following screening, height will be collected only for subjects ≤21 years of age on the date of informed consent.

<sup>g</sup> Subjects who are <18 years of age on the date of informed consent and who have completed at least 12 weeks of study drug treatment will have a single ophthalmologic examination conducted by a licensed ophthalmologist or optometrist at completion of study participation (defined in Section 9.1.6), except for those subjects who have withdrawn consent or assent. This examination should be completed within 4 weeks before the Week 24 Visit, unless the subject prematurely discontinues study drug, in which case this examination should occur by the Safety Follow-up Visit (or ETT Visit for subjects who do not complete a Safety Follow-up Visit). Refer to Section 11.7.6.



**Table 3-2 Study VX17-659-102: Treatment Period and Safety Follow-up Visit**

Event/Assessment <sup>a</sup>	Day 1	Day 15 (± 3 Days)	Week 4 (± 5 Days)	Week 8 (± 5 Days)	Week 12 (± 5 Days)	Week 16 (± 5 Days)	Week 20 (± 5 Days)	Week 24 (± 5 Days)	ETT Visit <sup>b</sup>	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug (If Applicable) <sup>c</sup>
Complete physical examination <sup>h</sup>	X		X					X	X	
Pregnancy testing <sup>i</sup>	urine	urine	urine	urine	urine	urine	urine <sup>j</sup>	urine	serum	serum
FSH <sup>k</sup>										
Standard 12-lead ECG <sup>l</sup>	X	X	X	X	X	X		X	X	X
Vital signs <sup>m</sup>	X	X	X	X	X	X		X	X	X
Pulse oximetry <sup>m</sup>	X	X	X	X	X	X		X	X	X
Spirometry <sup>n</sup>	X	X	X	X	X	X		X	X	X
Sweat chloride <sup>o</sup>	X		X	X	X			X	X	
Urinalysis	X							X	X	X
Hematology	X <sup>p</sup>	X	X	X	X	X		X	X	X
Coagulation	X <sup>p</sup>							X	X	X
Serum chemistry	X <sup>p</sup>	X	X	X	X	X		X	X	X
PK sampling <sup>q</sup>	X		X	X	X	X			X	

<sup>h</sup> Subjects will have a complete physical examination as defined in [Section 11.7.3](#). Symptom-directed physical examinations will occur at any time during the study if deemed necessary by the investigator.

<sup>i</sup> Any female subject who does not meet the criteria for non-childbearing potential is considered to be of childbearing potential and must have pregnancy tests at the indicated time points. A definition of non-childbearing potential is provided in [Section 11.7.7.1](#).

<sup>j</sup> At Week 20, when there is no clinic visit, a urine pregnancy test will be performed with a home kit provided by the study site. Results will be reported to the site by telephone.

<sup>k</sup> Blood samples for FSH will be measured as needed as outlined in [Section 11.7.2](#).

<sup>l</sup> All standard 12-lead ECGs will be performed after the subject has been at rest for at least 5 minutes. ECGs will be collected before dosing (as applicable).

<sup>m</sup> Vital signs and pulse oximetry will be collected before dosing and after the subject has been at rest for at least 5 minutes ([Section 11.7.3](#) and [Section 11.7.4](#)).

<sup>n</sup> Spirometry assessments must be performed before study drug dosing ([Section 9.6.1](#)) and should be performed pre-bronchodilator ([Section 11.6.1](#)) at approximately the same time at each visit.

<sup>o</sup> Sweat chloride collection will occur before study drug dosing ([Section 11.4](#)). At each time point, 2 samples will be collected, 1 from each arm (left and right).

<sup>p</sup> Blood samples will be collected before the first dose of study drug.

<sup>q</sup> PK samples will be collected predose on Day 1, Week 4, Week 8, Week 12, and Week 16. Approximately 40 subjects enrolled in the study will have 4 postdose samples taken at 2, 4, 6, and 8 hours after the morning dose at Week 4. All remaining subjects will have 1 postdose sample taken at 1 hour after the morning dose at Week 4. Vertex will manage the allocation of the 40 subjects providing more intensive PK sampling across study sites ([Section 11.3.1](#)). If study drug is not administered at the Week 4 Visit (i.e., due to study drug interruption or permanent discontinuation), a single PK blood sample will be collected at the visit. At the ETT Visit, a single PK blood sample will be collected.

**Table 3-2 Study VX17-659-102: Treatment Period and Safety Follow-up Visit**

Event/Assessment <sup>a</sup>	Day 1	Day 15 (± 3 Days)	Week 4 (± 5 Days)	Week 8 (± 5 Days)	Week 12 (± 5 Days)	Week 16 (± 5 Days)	Week 20 (± 5 Days)	Week 24 (± 5 Days)	ETT Visit <sup>b</sup>	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug (If Applicable) <sup>c</sup>
Randomization <sup>l</sup>	X									
Study drug dosing <sup>u</sup>	Day 1 through evening before Week 24									
Study drug count	X	X	X	X	X	X		X	X	
Other events related to outcome <sup>v, w</sup>	Continuous from signing of ICF through completion of study participation									
Medications review <sup>w</sup>	Continuous from signing of ICF through completion of study participation									
Treatments and procedures review <sup>w</sup>	Continuous from signing of ICF through completion of study participation									
AEs and SAEs <sup>w, x</sup>	Continuous from signing of ICF through completion of study participation									

AE: adverse event; CF: cystic fibrosis; CFQ-R: CF Questionnaire-Revised; ETT: Early Termination of Treatment; FSH: follicle-stimulating hormone; GPS: Global Patient Safety; ICF: informed consent form; PD: pharmacodynamic; PEx: pulmonary exacerbation(s); PK: pharmacokinetic; SAE: serious adverse event; [REDACTED]

[REDACTED]

Randomization may occur on either Day -1 or Day 1, after all eligibility criteria are confirmed.

<sup>u</sup> The study drug regimen should be administered as outlined in [Section 9.6.1](#). On days of scheduled visits, refer to [Section 9.6.1](#) for the timing of dosing relative to the assessment. The final dose of study drug will be administered the evening before the Week 24 Visit.

<sup>v</sup> Other events related to outcome include assessments relating to PEx, administration of antibiotic therapy for sinopulmonary signs/symptoms, and hospitalizations for CF ([Section 11.6.4](#)).

<sup>w</sup> Completion of study participation is defined in [Section 9.1.6](#).

<sup>x</sup> SAEs that occur after completion of study participation and are considered related to study drug will be reported to Vertex GPS within 24 hours as described in [Section 13.1.2.2](#).

[REDACTED]

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APPENDIX A Eligible MF *CFTR* Mutations



## List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
BMI	body mass index
CBC	complete blood count
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire - Revised
<i>CFTR</i>	CF transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
Cl <sup>-</sup>	chloride ion
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRO	contract research organization
█	█
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
█	█
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
ETT	Early Termination of Treatment
EU	European Union
<i>F508del</i>	<i>CFTR</i> gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F/F	homozygous for <i>F508del</i>
F/MF	heterozygous for <i>F508del</i> and a minimal CFTR function mutation
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
█	█
FEV <sub>1</sub>	forced expiratory volume in 1 second
FRT	Fischer rat thyroid
FSH	follicle-stimulating hormone
█	█
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLI	Global Lung Function Initiative
GPS	Global Patient Safety
HBE	human bronchial epithelial (cells)

<b>Abbreviation</b>	<b>Definition</b>
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
IA	interim analysis
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
█	█
█	█
IPD	important protocol deviation
IRB	institutional review board
IV	intravenous
IvA	ivacaftor
IWRS	interactive web response system
LLN	lower limit of normal
LUM	lumacaftor
M1-TEZ	metabolite of TEZ
MAA	Marketing Authorization Application
max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal CFTR function mutation
min	minimum value
MMRM	mixed-effects model for repeated measures
█	█
N	number of subjects
OATP1B1	organic anion transporting polypeptide 1B1
<i>P</i>	probability
PD	pharmacodynamic, pharmacodynamics
PE	physical examination
PE <sub>x</sub>	pulmonary exacerbation
PI	pancreatic insufficiency
PK	pharmacokinetic, pharmacokinetics
ppFEV <sub>1</sub>	percent predicted forced expiratory volume in 1 second
PR	PR interval, segment
PT	Preferred Term
q12h	every 12 hours
qd	once daily
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QT <sub>c</sub>	QT interval corrected
QT <sub>cF</sub>	QT interval corrected by Fridericia's formula
RR	interval from the onset of 1 QRS complex to the next

Abbreviation	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SI	SI units (International System of Units)
SOC	System Organ Class
SUSAR	suspected, unexpected, serious adverse reaction
SwCl	sweat chloride
TC	triple combination
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
[REDACTED]	[REDACTED]
ULN	upper limit of normal
US	United States
USA	United States of America
UV	ultraviolet
[REDACTED]	[REDACTED]

## 5 INTRODUCTION

### 5.1 Background

Cystic fibrosis (CF) is an autosomal recessive chronic disease with serious morbidities and frequent premature mortality. At present, there is no cure. CF affects approximately 70,000 individuals worldwide<sup>1</sup> (approximately 30,000 in the US<sup>1,2</sup> and 39,000 in the EU<sup>3</sup>). Based on its prevalence, CF qualifies as an orphan disease.<sup>4,5</sup>

CF is caused by decreased quantity and/or function of the CFTR protein due to mutations in the *CFTR* gene. The CFTR protein is an epithelial chloride channel that aids in regulating salt and water absorption and secretion and pH balance in sweat glands and multiple organs, including the lungs, pancreas, and other gastrointestinal organs. Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is approximately 40 years.<sup>2,6</sup> Progressive loss of lung function is the leading cause of mortality.<sup>7</sup> More effective treatments are needed for CF.

The most common disease-causing *CFTR* mutation, *F508del*, accounts for 70% of the identified alleles in people with CF<sup>8</sup>, and approximately 40% of people with CF are homozygous for *F508del* (F/F).<sup>2,3,8</sup>

Based on the understanding of the molecular defects caused by *CFTR* mutations, 2 complementary approaches have been developed to address the decreased quantity and/or function of CFTR in order to enhance chloride transport in patients with CF. Correctors facilitate the cellular processing and trafficking to increase the quantity of functional CFTR at the cell surface. Potentiators increase the channel open probability of the CFTR protein delivered to the cell surface to enhance ion transport. Depending on the amount of residual CFTR channel activity in the membrane, and the pathophysiology of that activity (reflecting the *CFTR* genotype of the patient and possibly other factors), both approaches may be required.

The therapeutic activity of CFTR correctors and potentiators has been established with products that were developed by Vertex and approved for the treatment of CF: ivacaftor (IVA) monotherapy (Kalydeco<sup>®</sup>), and lumacaftor (LUM) in combination with IVA (Orkambi<sup>®</sup>). Kalydeco and Orkambi are approved to treat CF in patients with specific *CFTR* genotypes. A second corrector/potentiator combination, tezacaftor (TEZ)/IVA (Symdeko<sup>®</sup>) is now approved in the US. An MAA has been submitted and is under review.

VX-659 is a next-generation CFTR corrector being developed for administration in triple combination (TC) with TEZ/IVA for the treatment of CF.

### 5.2 Rationale for the Present Study

This study will evaluate the efficacy and safety of VX-659 in TC with TEZ/IVA in subjects with CF who are heterozygous for *F508del* (F) and a second *CFTR* allele carrying a minimal function mutation that is non-responsive to TEZ, IVA, or TEZ/IVA (MF; refer to [Appendix A](#) for MF mutations). Patients with this genotype (F/MF patients) generally have severe disease and do not have approved CFTR modulator therapy available to them; previous studies with TEZ/IVA (Study VX14-661-107) and LUM/IVA (Study VX09-809-102) failed to demonstrate efficacy in this patient population. Due to this high unmet need, VX-659 is being developed in TC with TEZ/IVA for F/MF subjects. The potential for benefit in these patients is supported by in vitro

data and clinical data in F/MF subjects; in addition, the TC of VX-659/TEZ/IVA is generally safe and well tolerated (refer to VX-659 Investigator's Brochure).

## **6 STUDY OBJECTIVES**

### **6.1 Primary Objective**

To evaluate the efficacy of VX-659 in TC with TEZ and IVA in subjects with CF who are heterozygous for *F508del* and a minimal function mutation (F/MF subjects)

### **6.2 Secondary Objectives**

- To evaluate the safety of VX-659 in TC with TEZ and IVA
- To evaluate the pharmacodynamics (PD) of VX-659 in TC with TEZ and IVA
- To evaluate the pharmacokinetics (PK) of VX-659, TEZ, and IVA when administered in TC

## **7 STUDY ENDPOINTS**

### **7.1 Primary Endpoint**

Absolute change in ppFEV<sub>1</sub> from baseline at Week 4

### **7.2 Secondary Endpoints**

#### **7.2.1 Key Secondary Endpoints**

- Absolute change in ppFEV<sub>1</sub> from baseline through Week 24
- Number of pulmonary exacerbations (PEX) through Week 24
- Absolute change in SwCl from baseline through Week 24
- Absolute change in Cystic Fibrosis Questionnaire - Revised (CFQ-R) respiratory domain score from baseline through Week 24
- Absolute change in body mass index (BMI) from baseline at Week 24
- Absolute change in SwCl from baseline at Week 4
- Absolute change in CFQ-R respiratory domain score from baseline at Week 4

#### **7.2.2 Other Secondary Endpoints**

- Time-to-first PEX through Week 24
- Absolute change in BMI z-score from baseline at Week 24
- Absolute change in body weight from baseline at Week 24
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry
- PK parameters of VX-659, TEZ, M1-TEZ, and IVA

## 8 STUDY POPULATION

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

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

### 8.1 Inclusion Criteria

1. Subject (or his or her legally appointed and authorized representative) will sign and date an informed consent form (ICF), and, when appropriate, an assent form.
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Age 12 years or older, on the date of informed consent.
4. Confirmed diagnosis of CF as determined by the investigator.
5. Heterozygous for *F508del* and an MF mutation (F/MF genotypes, see [Appendix A](#) for eligible MF mutations). If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility. Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study ([Section 9.9](#)).
6. Forced expiratory volume in 1 second (FEV<sub>1</sub>) value  $\geq 40\%$  and  $\leq 90\%$  of predicted mean for age, sex, and height (equations of the Global Lung Function Initiative [GLI])<sup>9</sup> at the Screening Visit. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria<sup>10</sup> for acceptability and repeatability.
7. Stable CF disease as judged by the investigator.
8. Willing to remain on a stable CF treatment regimen (as defined in [Section 9.5](#)) through completion of study participation.

### 8.2 Exclusion Criteria

1. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This includes, but is not limited to, the following:
  - Clinically significant cirrhosis with or without portal hypertension
  - Solid organ or hematological transplantation.
  - Alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.

- Cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years)
2. Any of the following abnormal laboratory values at screening:
    - Hemoglobin <10 g/dL
    - Total bilirubin  $\geq 2 \times$  ULN
    - Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP)  $\geq 3 \times$  ULN
    - Abnormal renal function defined as glomerular filtration rate  $\leq 50$  mL/min/1.73 m<sup>2</sup> (calculated by the Modification of Diet in Renal Disease Study Equation)<sup>11,12</sup> for subjects  $\geq 18$  years of age and  $\leq 45$  mL/min/1.73 m<sup>2</sup> (calculated by the Counahan-Barratt equation)<sup>13</sup> for subjects aged 12 to 17 years (inclusive)
  3. An acute upper or lower respiratory infection, PEx, or changes in therapy (including antibiotics) for sinopulmonary disease within 28 days before the first dose of study drug (Day 1).
  4. Lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For subjects who have had a history of a positive culture, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
    - The subject has not had a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent.
    - The subject has had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent.
  5. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug (Day 1).
  6. Ongoing or prior participation in a study of an investigational treatment within 28 days or 5 terminal half-lives (whichever is longer) before screening. The duration of the elapsed time may be longer if required by local regulations.
  7. Use of prohibited medications as defined in [Table 9-2](#), within the specified window before the first dose of study drug (Day 1).
  8. Pregnant or nursing females. Females of childbearing potential must have a negative pregnancy test at screening (serum test) and Day 1 (urine test).
  9. 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 at that site. However, an adult (aged 18 years or older) who is a relative of a study staff member may be randomized in the study provided that
    - the adult lives independently of and does not reside with the study staff member, and



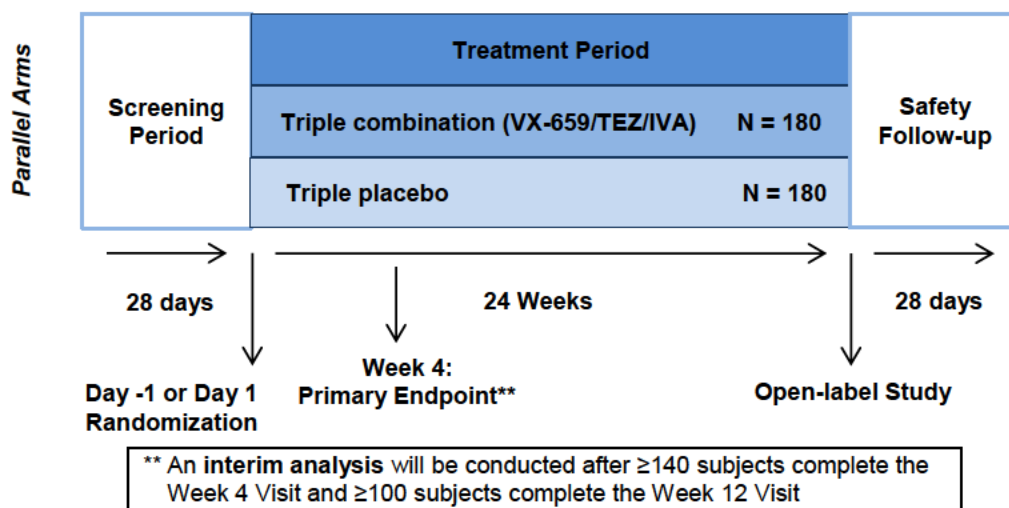
- the adult participates in the study at a site other than the site at which the family member is employed.

## 9 STUDY IMPLEMENTATION

### 9.1 Study Design

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

**Figure 9-1 Schematic of the Study Design**



IVA: ivacaftor; N: number of subjects; TEZ: tezacaftor

Notes: The figure is not drawn to scale. The Safety Follow-up Visit is not required for subjects who complete the Week 24 Visit and enroll in an open-label study within 28 days after the last dose of study drug (Section 9.1.3).

Study drug is defined in Section 10.

Approximately 360 subjects will be randomized (1:1) to the TC VX-659/TEZ/IVA arm or the triple placebo arm. The planned dosages to be evaluated are shown in Table 9-1. Randomization will be stratified; details are provided in Section 9.2.

**Table 9-1 Treatment Arms and Dosages**

Treatment Arm	VX-659 Dosage	TEZ Dosage	IVA Dosage
TC	240 mg qd	100 mg qd	150 mg q12h
Triple placebo	0 mg	0 mg	0 mg

IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TC: triple combination; TEZ: tezacaftor

Note: Study drug administration is described in Section 9.6.

Study visits and assessments to be conducted are shown in Table 3-1 and Table 3-2. All visits will occur within the windows specified.



### 9.1.1 Screening

The Screening Period (Day -28 through Day -1) will occur within 28 days before the first dose of study drug.

Screening assessments will be used to confirm that subjects meet the eligibility criteria. The investigator (or an appropriate authorized designee) will obtain informed consent and assent, if applicable, from each subject before any study procedure takes place.

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

Screening assessments may be repeated once to establish study eligibility. If repeat values of the individual assessment(s) are within the eligibility criteria and completed within the screening window, then the subject is eligible for the study.

#### 9.1.1.2 Rescreening

Subjects may be rescreened once. If a subject is rescreened, all screening assessments will be repeated, except for:

- *CFTR* genotyping
- Follicle-stimulating hormone (FSH) level (if serum FSH level was in the postmenopausal range as determined by the laboratory performing the test during prior screening)
- G6PD activity test
- Ophthalmologic examination (if performed within 3 months of the date of informed consent, for subjects <18 years of age )

If a subject is rescreened, a new screening window will begin when 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 for the following reasons:

- Repetition of the Screening Period assessments (Section 9.1.1.1)
- Unexpected operational or logistic delays, or to meet the eligibility criteria
- Scheduling of ophthalmologic examination (for subjects <18 years of age on the date of informed consent, [Section 11.7.6](#))
- 28-day washout period for subjects who have been on an investigational or commercially available *CFTR* modulator (e.g., TEZ/IVA, IVA [Kalydeco], LUM/IVA [Orkambi]; see [Table 9-2](#)).

### 9.1.2 Treatment Period

The Treatment Period will be randomized, double-blind, and placebo-controlled. It will last approximately 24 weeks (Day 1 through Week 24). Study drug administration details are provided in [Section 9.6](#).

Randomization will occur before the first dose of study drug during the Treatment Period and may occur on either Day 1 or Day -1. Randomization and stratification details are provided in [Section 9.2](#).

Subjects who prematurely discontinue study drug treatment will remain in the study from the time of discontinuation of study drug treatment through the last scheduled study visit and complete the assessments for all study visits, as described in Section 9.1.4.

### **9.1.3 Follow-up**

The Safety Follow-up Visit will occur approximately 28 days after the last dose of study drug for subjects who complete study drug dosing and for subjects who prematurely discontinue study drug dosing, as described in Section 9.1.4.

An open-label study will be available for subjects who complete the Week 24 Visit and are eligible. The Safety Follow-up Visit is not required for subjects who complete the Week 24 Visit and enroll in an open-label study within 28 days after the last dose of study drug.

### **9.1.4 Early Termination of Treatment**

If a subject prematurely discontinues study drug treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the decision to discontinue treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 days after their last dose of study drug. The assessments performed at the Safety Follow-up Visit are listed in [Table 3-2](#).

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

Subjects who prematurely discontinue study drug treatment will continue to complete all scheduled study visits for assessments following completion of the ETT Visit, as detailed in [Table 3-2](#). Data regarding concomitant antibiotic therapy for sinopulmonary signs/symptoms will also continue to be collected for these subjects.

If a subject withdraws from the study and also withdraws consent or assent, no further assessments will be performed. Vertex may retain and continue to use any data and samples collected before such withdrawal of consent or assent.

### **9.1.5 Lost to Follow-up**

A subject will be considered lost to follow-up if both of the following occur:

- The subject misses 2 consecutive study visits (telephone contact and/or clinic visit) and is subsequently unable to be contacted by telephone (3 documented attempts by telephone within 2 weeks following the second missed visit)
- The subject does not respond within 2 weeks to a registered letter sent after the 3 attempted telephone contacts.

### **9.1.6 Completion of Study Participation**

Completion of study participation for each individual subject is defined as one of the following:

- For subjects who complete the Treatment Period and enter an open-label study within 28 days of the Week 24 Visit: the Week 24 Visit
- For subjects who complete the Treatment Period and do not enter an open-label study within 28 days of the Week 24 Visit: the Safety Follow-up Visit
- For subjects who prematurely discontinue study drug treatment but do not withdraw consent (and assent, as applicable): the latest of the Week 24 Visit, ETT Visit, or Safety Follow-up Visit (if required)
- For subjects who withdraw consent or assent: date of withdrawal of consent or assent, whichever is earlier ([Section 9.9](#))

If subjects are lost to follow-up ([Section 9.1.5](#)), the date of completion of study participation will be defined as the date of the last contact.

The end of study is defined in [Section 13.2.8](#).

### **9.1.7 Independent Data Monitoring Committee**

This study will be monitored by an independent data monitoring committee (IDMC), which will conduct periodic planned safety review(s) of study data and the planned efficacy interim analysis (IA) ([Section 12.3.6.2](#)). Procedural details of the IDMC 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**

Subjects will be randomized (1:1) to the TC VX-659/TEZ/IVA arm or to the triple placebo arm. Randomization will be stratified by ppFEV<sub>1</sub> determined during the Screening Period (<70 versus ≥70), age at the Screening Visit (<18 versus ≥18 years of age), and sex (male versus female).

An interactive web response system (IWRS) will be used to assign subjects to treatment. The randomization code list will be produced by Vertex Biometrics or a qualified randomization vendor.

## **9.3 Rationale for Study Design and Study Drug Regimens**

### **9.3.1 Study Design**

This Phase 3 study will assess the efficacy, safety, PD, and PK of VX-659/TEZ/IVA TC therapy in subjects with CF who have F/MF genotypes.

A randomized, double-blind, controlled study design was selected to ascertain the effects of VX-659/TEZ/IVA while avoiding observer bias. Placebo is considered the appropriate comparator because efficacy has not been established for a corrector, potentiator, or any corrector/potentiator combination in subjects with F/MF genotypes.

This study will have a 24-week treatment duration to allow for the collection of placebo-controlled safety data for this duration and the collection of data for outcomes that require longer treatment durations to demonstrate an effect (e.g., PEx and changes in nutritional status).

The primary endpoint is the absolute change in ppFEV<sub>1</sub> at Week 4. Previous studies of CFTR modulators (IVA, LUM/IVA, and TEZ/IVA) have demonstrated that efficacy related to lung

function (ppFEV<sub>1</sub>) can be reliably established using an endpoint at Week 4. In these studies, rapid improvements in ppFEV<sub>1</sub> are observed by Day 15, with a separation between the active treatment and placebo groups that is sustained through 24 weeks of treatment. These studies were conducted in patients with different genotypes, baseline ppFEV<sub>1</sub>, and age groups, using CFTR modulators that had different magnitudes of response.

### 9.3.2 Study Drug Dose

#### VX-659 Dosage

A VX-659 dose of 240 mg qd was selected for the current study based on an assessment of the benefit-risk profile from the ongoing Phase 2 Study VX16-659-101 (Study 659-101) Part 1,

#### TEZ and IVA Dosages

TEZ will be administered as 100 mg qd and IVA will be administered as 150 mg q12h. This is the approved dosing regimen for Symdeko, which is now approved in the US.

### 9.3.3 Rationale for Study Population

This study will enroll subjects with CF with F/MF genotypes. As described in [Section 5.2](#), patients with F/MF genotypes have unmet need and are expected to respond to a TC regimen of VX-659/TEZ/IVA based on results from Phase 1 and 2 studies conducted in F/MF subjects, in vitro experiments in relevant human F/MF cell-based model systems, and preliminary results from Phase 1 and 2 studies with VX-659/TEZ/IVA.

The VX-659 Phase 2 clinical safety and efficacy data support the enrollment of pediatric subjects  $\geq 12$  and  $< 18$  years of age in this study.

### 9.3.4 Rationale for Study Assessments

The PD and efficacy endpoints being evaluated (SwCl, spirometry, PEx, anthropometric measurements, and patient-reported outcomes) are widely accepted and generally recognized as reliable, accurate, and relevant to the study of individuals with CF. SwCl was evaluated in the registration study of IVA (Kalydeco), and spirometry and CFQ-R assessments were evaluated in the registration studies of IVA (Kalydeco) and LUM/IVA combination therapy (Orkambi).

[REDACTED]

[REDACTED]

[REDACTED]

**9.4 Study Restrictions**

**9.4.1 Prohibited Medications**

[Table 9-2](#) lists prohibited medications. A non-exhaustive list of study prohibitions and cautions for medication will be provided in the Study Reference Manual.

**Table 9-2 Prohibited Medications**

Medication	Timing of Restriction		Rationale
	Start of Restriction	End of Restriction	
Moderate and strong CYP3A or CYP2C9 inducers	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through completion of study participation	VX-659, TEZ, and IVA are metabolized extensively via CYP3A4. VX-659 is also metabolized by CYP2C9. Therefore, use of moderate and strong inducers of CYP3A or CYP2C9 and moderate and strong inhibitors of CYP3A, which have the potential to alter the exposure of VX-659, TEZ, or IVA, will be prohibited.
Moderate and strong CYP3A inhibitors (except ciprofloxacin) <sup>a</sup>	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through completion of study participation	
Sensitive OATP1B1 substrates	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through completion of study participation	VX-659 is a potential inhibitor of the hepatic transporter OATP1B1. Therefore, sensitive substrates of OATP1B1, such as HMG-CoA reductase inhibitors (“statins”) are prohibited during treatment.
CFTR modulators (investigational or approved), except for study drugs	None allowed within 28 days before the first dose of the study drug on Day 1	None allowed until after the last dose of study drug	These agents may confound the results of this study.

CYP: cytochrome P450; IVA: ivacaftor; OATP1B1: organic anion transporting polypeptide 1B1; TEZ: tezacaftor

<sup>a</sup> Ciprofloxacin is not a moderate CYP3A inhibitor on the basis of results of a drug-drug interaction study conducted with IVA, a sensitive CYP3A substrate (Kalydeco [ivacaftor] US Package Insert).

#### 9.4.2 Exposure to Sunlight

Subjects will take appropriate measures to minimize exposure to UV radiation (e.g., prolonged sunlight, tanning booths) from Day 1 through completion of study participation.

#### 9.5 Prior and Concomitant Medications

Information regarding prior and concomitant medications, including CF medications, other medications, and herbal and naturopathic remedies, will be collected from each subject’s source documentation for medications taken within 56 days before the Screening Visit through completion of study participation, as defined in [Section 9.1.6](#).

For subjects who are screened but are not subsequently randomized, details of prior medication will be documented only in the subjects’ source documents.

- Subjects should remain on a stable treatment regimen for their CF from 28 days before the Day 1 Visit through completion of study participation. Stable treatment regimen is defined as the current treatment regimen for CF that subjects have been following for at least 28 days before the Day 1 Visit. Subjects should not initiate long-term treatment with new medication from 28 days before the Day 1 Visit through completion of study participation. Guidelines for stable treatment regimens for CF are as follows:
  - o Subjects who are taking inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.

- o Subjects who cycle onto and off of an inhaled antibiotic should continue on their prior schedule. The timing of the first dose of study drug on the Day 1 Visit should be synchronized as closely as possible (e.g., not more than  $\pm 3$  days) to the first day in the cycle onto the inhaled antibiotic.
- o Subjects who alternate between 2 different inhaled antibiotics should remain on the same cycling schedule during the study. The timing of the first dose of study drug on the Day 1 Visit should be synchronized as closely as possible (e.g., not more than  $\pm 3$  days) to the first day in the cycle onto 1 of the inhaled antibiotics.
- Subjects may receive doses of prednisone or prednisolone of up to 10 mg/day chronically, or up to 60 mg daily for up to 5 days.
- 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 11.6.1](#).

## **9.6 Administration**

### **9.6.1 Dosing**

Study drug will be administered orally. All subjects will receive the same number of tablets each day to maintain the blind. Additional information is provided in the Pharmacy Manual.

Study drug will be administered with a fat-containing meal or snack, such as a standard “CF” meal or snack or a standard meal.

1. It is recommended that the dose be taken within 30 minutes of the start of the meal or snack.
2. Study drug will be administered as 2 fixed-dose combination (FDC) TC or placebo tablets in the morning and as 1 IVA or placebo tablet in the evening. For each subject, doses of study drugs will be taken at approximately the same time ( $\pm 2$  hours) each day.
3. The date, amount taken, and time of study drug administration, including whether food was taken with each dose, will be recorded for the 2 doses before PK sample collection and the dose received on the morning of PK sample collection.
4. On days of scheduled visits, the morning dose of study drug (TC or placebo) 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 TC or placebo.
5. If a subject’s scheduled visit is to occur in the afternoon, the following guidelines must be used:
  - If the dose in the clinic will be within 6 hours of the subject’s scheduled morning dose, the subject should withhold their morning dose of TC or placebo 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 of TC or placebo at home.
  - At the Week 4 Visit, the morning dose of TC or placebo must be administered in the clinic to enable post-dose PK sampling relative to the morning dose.



6. Subjects will be instructed to bring all used and unused materials associated with the study drug to the site; study drug will be dispensed at each visit, as appropriate.

## **9.6.2 Missed Doses**

### **9.6.2.1 Morning Dose of Study Drug**

If a subject misses the morning dose of study drug (TC or placebo) and recalls within 6 hours, the subject should take his/her dose with food. If more than 6 hours but fewer than 12 hours have elapsed after his/her usual dosing time, the subject should take the morning dose of TC or placebo but skip the evening dose of study drug (IVA or placebo). If more than 12 hours have elapsed after his/her usual dosing time, the subject should skip the morning dose of TC or placebo and take the evening dose of IVA or placebo.

### **9.6.2.2 Evening Dose of Study Drug**

If a subject misses the evening dose of IVA or placebo and recalls 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.

## **9.7 Dose Modification for Toxicity**

No dose modifications for toxicity are allowed. Treatment may be interrupted as outlined in Section 9.8. If any unacceptable toxicity arises, individual subjects will discontinue dosing ([Section 9.1.4](#)).

## **9.8 Study Drug Interruption and Stopping Rules**

The medical monitor should be notified of an interruption of study drug that lasts >72 hours for any reason and of the resumption of study drug after such interruption.

### **9.8.1 Liver Function Tests**

The central laboratory will notify the medical monitor of ALT or AST  $>3 \times$  ULN and total bilirubin  $>2 \times$  ULN that are derived from centrally submitted samples.

Subjects with new treatment-emergent ALT or AST elevations of  $>3 \times$  ULN, with or without total bilirubin  $>2 \times$  ULN, must be followed closely, including confirmatory testing performed by the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT, AST, and bilirubin levels, as clinically indicated.

If a subject cannot return to the site for confirmatory testing, a local laboratory may be used. Local laboratory results 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 administration **must be interrupted** immediately (prior to confirmatory testing) if any of the following criteria are met:

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

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

Study drug administration **must be discontinued** if the following criterion is met:

- Subsequent ALT or AST values confirm the initial elevation that satisfied the interruption rule (above), and no convincing alternative etiology (e.g., acetaminophen use, viral hepatitis, alcohol ingestion) is identified, regardless of whether transaminase levels have improved

All subjects in whom treatment is discontinued for elevated transaminases (and bilirubin, as applicable) should have these levels monitored closely until levels normalize or return to baseline.

If an alternative, reversible cause of transaminase elevation with or without increased bilirubin or clinical jaundice has been identified, study drug administration may be resumed once transaminases return to baseline or are  $\leq 2 \times$  ULN, whichever is higher. Regardless of the duration of interruption, the medical monitor should be notified prior to resumption of study drug. Upon resumption of study drug, transaminases and bilirubin should be assessed weekly for 4 weeks. If a protocol-defined transaminase elevation interruption threshold recurs 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.

### **9.8.2 Rash**

Individuals who develop a generalized rash will be monitored closely. Study drug dosing should be interrupted if a subject develops a generalized rash of Grade 3 or higher, or a rash that is considered a serious adverse event. The investigator will notify the medical monitor of any rash that results in interruption of study drug, is Grade 3 or higher ([Section 13.1.1.4](#)), or is a serious adverse event (SAE). Investigators should consider additional evaluation including laboratory testing (e.g., complete blood count [CBC] with differential, LFTs), photographs of the rash, and dermatology consultation. The investigator may consider resumption of study drug if considered clinically appropriate.

### **9.9 Removal of Subjects**

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

In addition, a subject must be discontinued from study drug treatment if the subject meets any of the following criteria:

- Has a screening *CFTR* genotype that does not confirm study eligibility if a previous *CFTR* genotype laboratory report was used to establish eligibility. These subjects must be discontinued from the study ([Section 8.1](#))
- Meets any of the stopping (discontinuation) criteria ([Section 9.7](#))
- Becomes pregnant ([Section 11.7.7.2](#))

Subjects who discontinue study drug treatment should return for study assessments, as noted in [Section 9.1.4](#).

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 an ETT Visit and Safety Follow-up Visit, if applicable (see [Section 9.1.4](#)), and follow up with the subject regarding any unresolved AEs.

If the subject withdraws consent or assent for the study, no further assessments will be performed. 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.

#### **9.10 Replacement of Subjects**

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

Subjects who withdraw or are withdrawn for nonsafety reasons during the study drug Treatment Period may be replaced at Vertex's discretion.

### **10 STUDY DRUG INFORMATION AND MANAGEMENT**

Study drug refers to VX-659/TEZ/IVA, IVA, and their matching placebos.

#### **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 study drug will be in the Pharmacy Manual.

#### **10.3 Study Drug Supply, Storage, and Handling**

VX-659/TEZ/IVA will be supplied as 2 FDC film-coated tablets (120 mg VX-659/50 mg TEZ/75 mg IVA). Matching VX-659/TEZ/IVA placebo tablets will be of similar size and appearance and contain 0-mg VX-659, 0-mg TEZ, and 0-mg IVA ([Table 10-1](#)).

IVA (150 mg) will be supplied as tablets containing 150-mg IVA. Matching IVA placebo tablets will be of similar size and appearance and contain 0-mg IVA ([Table 10-1](#)).

Blister cards must be stored under conditions noted in the Pharmacy Manual. 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 via the drug accountability forms as instructed by Vertex.

**Table 10-1 Study Drug: Strength/Dosing Form/Route**

<b>Drug Name, Dosing Form, Route</b>	<b>Strength</b>
VX-659/TEZ/IVA, FDC tablet, oral	
VX-659	120 mg
TEZ	50 mg
IVA	75 mg
VX-659/TEZ/IVA-matching placebo, tablet, oral	0 mg
IVA, tablet, oral	150 mg
IVA-matching placebo, tablet, oral	0 mg

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

#### **10.4 Drug Accountability**

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of (1) study drug received; (2) study drug dispensed to the subjects; 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. The study monitor will review study drug records and inventory throughout the study.

If a site uses a site-specific drug accountability system and/or process, including processes associated with the destruction of returned materials, the process must be documented and approved by Vertex. The study monitor must review the drug accountability documentation on a regular basis. The study monitor will promptly communicate to Vertex any discrepancies he/she is unable to resolve with the site.

#### **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. 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 should consider discontinuing the subject from the study.

#### **10.7 Blinding and Unblinding**

This will be a double-blind study.

### 10.7.1 Blinding

All subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team will be blinded to the treatment codes.

Individuals who may be unblinded include only the following:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the subject and her fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy serious adverse event (SAE) processing and reporting regulations
- Vendor preparing the final (production) randomization list
- Vertex IWRS Manager
- Vertex Clinical Supply Chain
- IDMC
- External independent biostatistician preparing the unblinded analysis for review by the IDMC
- Bioanalytical contract research organization (CRO) analyzing PK samples and the Vertex Bioanalytical personnel who is not a member of the study team but reviews raw data from the Bioanalytical CRO. The Vertex Bioanalytical study team member will continue to be blinded.
- Vendor for modeling and simulations performing population PK modeling in preparation for regulatory submission(s)

For the purpose of regulatory submissions, a limited Vertex team may be unblinded to the IA if the IDMC declares that the study has crossed the efficacy boundary ([Section 12.3.6.1](#)). Members of the limited Vertex unblinded team will not be involved in or influence the conduct of the remaining part of the study to protect the integrity of the study.

#### Access to Spirometry and SwCl Results:

During the conduct of the study, the Vertex study team will not have access to the spirometry or SwCl results after the morning dose on Day 1.

Shortly before any planned efficacy analysis is conducted, the spirometry and SwCl data will be reviewed for data cleaning purposes by a biostatistician who does not have access to the treatment codes.

Individual SwCl test results will not be disclosed to the study sites with the exception of the screening values. Subjects and their parents/caregivers/companions should not be informed of study-related spirometry results until Vertex has determined that the study has completed (i.e., clinical study report [CSR] finalization), regardless of whether the subject has prematurely discontinued treatment.

## 10.7.2 Unblinding

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

### **Unblinding of Individual Subject Treatment Assignments by Investigator for Medical Emergencies or Urgent Clinical Situations**

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

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

In addition, the Vertex Medical Information Call Center (██████████) 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](#).

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

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

### **Unblinding: Interim Analysis**

The IA will be performed by an external independent biostatistician who is not involved in and will not influence study conduct. The analyses generated by the external independent biostatistician will then be reviewed by the IDMC. If the IDMC declares that the study has crossed the prespecified efficacy boundary ([Section 12.3.6.1](#)), then the study may be unblinded by a limited Vertex team to prepare a regulatory submission(s). Members of the limited Vertex unblinded team will not be involved in or influence the conduct of the remaining part of the

study to protect the integrity of the study. Regardless of the outcome of the IA, the study will continue through Week 24, and the subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team will remain blinded until the final database lock.

## 11 ASSESSMENTS

### 11.1 Timing of Assessments

The timing of assessments is shown in [Table 3-1](#) and [Table 3-2](#).

### 11.2 Subject and Disease Characteristics

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

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

### 11.3 Pharmacokinetics

#### 11.3.1 Blood Sampling

Blood samples will be collected to determine plasma concentrations of VX-659, TEZ, M1-TEZ, and IVA. [REDACTED]

Approximately 40 subjects enrolled in the study will have 4 postdose samples taken at 2, 4, 6, and 8 hours after the morning dose at Week 4. All remaining subjects will have 1 postdose sample taken at 1 hour after the morning dose at Week 4. Vertex will manage the allocation of the 40 subjects providing more intensive PK sampling across study sites.

All efforts should be made to obtain the PK samples at the exact nominal time relative to dosing. Acceptable windows for sampling times are shown in [Table 11-1](#). Samples collected outside of these acceptable windows will be considered protocol deviations.

**Table 11-1 Acceptable Pharmacokinetic Sampling Windows**

Sampling Time	Time From Scheduled Sampling Allowed
Predose	-60 minutes
From 0.25 up to ≤8 hours after study drug dosing	± 15 minutes

For each visit with a PK blood draw, a record of study drug administration will be collected as described in [Section 9.6](#). The collection date and exact time that each PK blood sample is drawn will also be recorded.

Samples from the PK sampling will be kept frozen by Vertex or its designee until all analyses have been completed and then disposed of according to Vertex or designee standard operating procedures.

Plasma concentration samples collected from subjects treated with placebo will not be routinely analyzed.

### **11.3.2 Processing and Handling of Pharmacokinetic Samples**

Detailed procedures for the collection of blood samples and further procedures for processing and handling of samples for PK analysis will be provided in the PK Sample Handling Guidelines.

### **11.3.3 Bioanalysis**

Samples will be analyzed using validated analytical methods in compliance with Vertex or designee standard operating procedures. A description of the assays and validation data will be provided in separate reports.

### **11.4 Pharmacodynamics: Sweat Chloride**

SwCl samples will be collected with an approved collection device. Each collection will occur before study drug dosing ([Section 9.6.1](#)). At each time point, 2 samples will be collected, 1 from each arm (left and right). Sweat samples will be sent to a central laboratory for testing and interpretation of results. Specific instructions for the collection, handling, processing, and shipping of SwCl samples to the central laboratory will be provided separately.

See [Section 10.7.1](#) for information about access to SwCl results.



## **11.6 Efficacy**

### **11.6.1 Spirometry**

Spirometry will be performed according to the American Thoracic Society Guidelines/European Respiratory Society Guidelines<sup>10</sup> and according to the additional guidelines that follow.

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

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

During the Screening Period, spirometry assessments may be performed pre- or post-bronchodilator. At all other visits, all spirometry assessments should be performed pre-bronchodilator. During the Treatment Period, spirometry assessments must be performed before study drug dosing ([Section 9.6.1](#)) at approximately the same time at each visit. In the event that a subject forgets to withhold bronchodilator(s), spirometry should be performed according to the following:

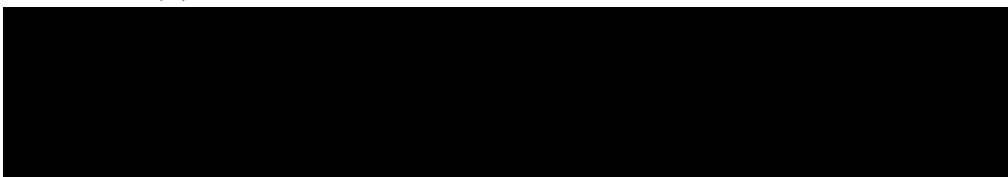
- If a subject's Day 1 spirometry assessment is pre-bronchodilator, but, on a subsequent visit, the subject forgets to withhold bronchodilator use, a post-bronchodilator spirometry assessment will be obtained for that visit only, and the visit will not be rescheduled.
- If, on Day 1, the subject forgets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

All sites will be provided with spirometers to be used for all study assessments. Spirometry data will be transmitted to a centralized spirometry service for quality review. The investigator's assessment of the spirometry results will be used for the screening assessment and determination of eligibility.

See [Section 10.7.1](#) for information about access to spirometry results.

The measured spirometric values listed below will be converted to percent predicted values using the standard equations of GLL.<sup>9</sup>

- FEV<sub>1</sub> (L)



### **11.6.2 Height and Weight**

Height and weight will be measured with shoes off. Following screening, height will be collected only for subjects  $\leq 21$  years of age on the date of informed consent.

### **11.6.3 Cystic Fibrosis Questionnaire-Revised**

The questionnaires provide information about demographics; general quality of life, school, work, or daily activities; and symptom difficulties (pertaining to CF).

Subjects will be asked to complete the CFQ-R in their native language, if validated translations are available.<sup>15, 16</sup> If there is no validated translation available in the subject's native language, the subject will not complete the questionnaire. Copies of the CFQ-R used 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.<sup>17, 18</sup>

The CFQ-R will be completed before any other assessments are performed at that visit.

Subjects who are 12 and 13 years of age at the date of informed consent will complete the CFQ-R Child version themselves, and their parents/caregivers will complete the CFQ-R Parent version, at all visits, regardless of whether the subject subsequently turns 14 years of age during the study. Subjects 14 years of age and older at the date of informed consent will complete the Adolescent/Adult version of the questionnaire themselves at all visits.

#### **11.6.4 Other Events Related to Outcome**

##### **11.6.4.1 Antibiotic Therapy for Sinopulmonary Sign/Symptoms**

New or changed antibiotic therapy (IV, inhaled, or oral) for the following sinopulmonary signs/symptoms will be determined and documented at visits as indicated in [Table 3-2](#):

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature above 38°C (equivalent to approximately 100.4°F)
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination (PE) of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

**For this study, PEx is defined as a new or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the above signs/symptoms.** This definition is based on the definition of a PEx used in previous clinical studies, including IVA clinical studies.<sup>19, 20</sup>

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

##### **11.6.4.2 Hospitalization for CF**

Subjects will be queried about planned and unplanned hospitalizations lasting  $\geq 24$  hours that occurred during the study. The dates of hospitalizations and the reasons for hospitalizations will be documented.

For any hospitalization (planned and unplanned), the procedures for safety reporting should also be followed.

## **11.7 Safety**

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

For subjects <18 years of age on the date of informed consent, ophthalmological examinations will also be performed at screening (if not done within preceding 3 months) and at Week 24 (or ETT Visit or Safety Follow-up Visit).

### **11.7.1 Adverse Events**

All AEs will be assessed, documented, and reported in accordance with ICH GCP guidelines.

[Section 13.1](#) outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting AEs. A separate document that details AE case report form (CRF) completion guidelines for investigators as well as training will be provided.

### **11.7.2 Clinical Laboratory Assessments**

Blood and urine samples will be analyzed at a central laboratory, with the exception of the urine pregnancy tests. As described below, urine pregnancy tests will either be analyzed by the site or at home using a home kit. On Day 1, blood samples will be collected before the first dose of the study drug.

Laboratory test results that are abnormal and considered clinically significant will be reported as AEs.

The safety laboratory test panels are shown in [Table 11-2](#).



**Table 11-2 Safety Laboratory Test Panels**

Serum Chemistry	Hematology	Urinalysis <sup>a</sup>
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen <sup>b</sup>	Erythrocytes	Nitrite
Creatinine	Mean corpuscular volume	Urobilinogen
Sodium	Platelets	Urine protein
Potassium	Reticulocytes	pH
Calcium	Leukocytes	Urine blood
Chloride	Differential (absolute and percent):	Specific gravity
Magnesium	Eosinophils	Urine ketones
Bicarbonate	Basophils	Urine bilirubin
Inorganic phosphate	Neutrophils	Urine glucose
Total and direct bilirubin	Lymphocytes	
Alkaline phosphatase	Monocytes	
Aspartate transaminase	<b>Coagulation Studies</b>	
Alanine transaminase	Activated partial thromboplastin time	
Amylase	Prothrombin time	
Lipase	Prothrombin time International	
Gamma-glutamyl transferase	Normalized Ratio	
Protein		
Albumin		
Creatine kinase		
Total cholesterol		
Lactate dehydrogenase		

Note: Haptoglobin may be analyzed if judged to be clinically appropriate by the investigator.

<sup>a</sup> If urinalysis results are positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be performed, and results will be provided for leukocytes, erythrocytes, crystals, bacteria, and casts.

<sup>b</sup> If blood urea nitrogen cannot be collected, urea may be substituted.

**Pregnancy ( $\beta$ -human chorionic gonadotropin) Tests for Females of Childbearing Potential:** Any female subject who does not meet the criteria for non-childbearing potential is considered to be of childbearing potential and must have a serum pregnancy test at screening. A definition of non-childbearing potential is provided in [Section 11.7.7.1](#). Serum pregnancy tests will be performed at the study site and analyzed at the central laboratory. Urine pregnancy tests will either be performed and analyzed at the site or, when there is no clinic visit scheduled, at home by using a home kit provided by the site. Results will be reported to the site by telephone. The urine pregnancy test on Day 1 must be negative before the first dose of study drug. Additional pregnancy tests may be required according to local regulations and/or requirements.

**FSH:** Blood samples for FSH will be measured as needed for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be in the postmenopausal range as determined by the laboratory performing the test.

**CFTR Genotype (Screening Period Only):** CFTR genotyping will be performed for all subjects. If the screening CFTR genotype result is not received before randomization, a previous CFTR genotype laboratory report may be used to establish eligibility. Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study ([Section 9.9](#)).

**G6PD Activity Test (Screening Period Only):** A blood sample will be collected for a quantitative G6PD activity assay, which will be performed in an established laboratory that runs the assay routinely. The use of a local laboratory that routinely runs the assay is permissible following approval by the medical monitor. In the event of a low G6PD activity result, the site will notify the Medical Monitor.

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

For the purposes of study conduct and unless noted otherwise (e.g., G6PD activity test), 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.

### **11.7.3 Physical Examinations and Vital Signs**

A PE of all body systems and vital signs assessment will be performed at screening and select study visits (see [Table 3-1](#) and [Table 3-2](#)). At other visits, symptom-directed PEs and symptom-directed vital sign assessments will occur at any time if deemed necessary by the investigator or healthcare provider.

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

Vital signs include blood pressure (systolic and diastolic), temperature (oral), pulse rate, and respiration rate. These will be assessed before dosing and following at least a 5-minute rest.

### **11.7.4 Pulse Oximetry**

Pulse oximetry is a noninvasive measure of oxygen delivery to the tissues and has been correlated with clinical status and lung function. Arterial oxygen saturation by pulse oximetry will be assessed following at least a 5-minute rest and before study drug dosing. At visits when study drug is taken at the site, pulse oximetry will be collected before study drug dosing ([Section 9.6.1](#)).

### **11.7.5 Electrocardiograms**

Standard 12-lead ECGs will be performed using a machine with printout according to the schedule of assessments ([Table 3-1](#) and [Table 3-2](#)). Additional standard 12-lead ECGs will be performed at any other time if clinically indicated. Subjects will be instructed to rest for at least 5 minutes before having an ECG performed.

The ECG traces will be manually read at the study site. A printout of the ECG traces will be made for safety review by the investigator and maintained with source documentation. Clinically significant ECG abnormalities occurring during the study through completion of study participation will be recorded as AEs.

To ensure the safety of the subjects, a qualified individual at the study site will make comparisons to baseline measurements. If the QTcF is increased by >60 msec from the baseline or an absolute QTcF value is  $\geq 500$  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 (>60 msec from baseline or  $\geq 500$  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. Further details pertaining to ECGs will be provided to sites in the ECG Manual.

### 11.7.6 Ophthalmologic Examination

Ophthalmologic examinations will be conducted only for subjects who are <18 years of age on the date of informed consent. The examination does not need to be completed if there is documentation of bilateral lens removal for the subject.

All examinations will be conducted by a licensed ophthalmologist or optometrist and will include:

- 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 conducted if there is documentation of an examination meeting the protocol requirements that was conducted within 3 months before the date of informed consent.

In addition to the screening ophthalmologic examination, subjects who are <18 years of age on the date of informed consent and who have completed at least 12 weeks of study drug treatment will have a single ophthalmologic examination at completion of study participation (defined in [Section 9.1.6](#)), except for those subjects who have withdrawn consent or assent. This examination should be completed within 4 weeks before the Week 24 Visit, unless the subject prematurely discontinues study drug, in which case this examination should occur by the Safety Follow-up Visit (or ETT Visit for subjects who do not complete a Safety Follow-up Visit), as described in [Table 3-2](#).

Any clinically significant abnormal findings will be reported as AEs.

### 11.7.7 Contraception and Pregnancy

The effects of VX-659 monotherapy or in TC with TEZ and IVA on conception, pregnancy, and lactation in humans are not known. VX-659, TEZ, and IVA did not show genotoxic potential in a standard battery of in vitro (Ames test, chromosomal aberration, or micronucleus in cultured mammalian cells) and in vivo (rodent micronucleus) studies. Reproductive toxicology studies of VX-659, TEZ, and IVA have not shown teratogenicity in rats and rabbits.

#### 11.7.7.1 Contraception

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

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. True abstinence must be practiced from the Screening Visit through 90 days after the last dose of study drug.

- If the male is infertile (e.g., bilateral orchiectomy). If a male subject is assumed to have complete bilateral absence of the vas deferens, infertility must be documented before the first dose of study drug (e.g., examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound).
- If the female is of non-childbearing potential. To be considered of non-childbearing potential, the female must meet at least 1 of the following criteria:
  - o Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum FSH level within the laboratory’s reference range for postmenopausal females
  - o Documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy

Note: All other females (including females with tubal ligations) will be considered to be of childbearing potential.

- Same-sex relationships

**For subjects for whom the contraception requirement is not waived**, study participation requires a commitment from the subject that at least 1 acceptable method of contraception is used as a couple. Methods of contraception must be in successful use from signing of consent (or assent, when applicable), approximately 28 days before the first dose of study drug (unless otherwise noted), and until 90 days following the last dose of study drug. Additional contraception requirements may need to be followed according to local regulations and/or requirements. Acceptable methods of contraception are listed in Table 11-3.

**Table 11-3 Acceptable Methods of Contraception**

	<b>Male Subjects and Their Female (Non-study) Partners</b>	<b>Female Subjects and Their Male (Non-study) Partners</b>
Vasectomy performed at least 6 months previously, with a documented negative postvasectomy semen analysis for sperm	Yes	Yes
Bilateral tubal occlusion (e.g., ligation) performed at least 6 months previously	Yes	Yes
Male or female condom with or without spermicide <sup>a</sup>	Yes	Yes
Female barrier contraception (such as diaphragm, cervical cap, or sponge) with spermicide	Yes	Yes
Continuous use of an intrauterine device for at least 90 days before the first dose of study drug		
<b>Hormone-releasing</b>	Yes	<b>No<sup>b</sup></b>
Non-hormone releasing	Yes	Yes
<b>Hormonal</b> contraceptives, if successfully used for at least 60 days before the first dose of study drug	Yes	<b>No<sup>b</sup></b>

<sup>a</sup> A female condom cannot be used with a male condom due to risk of tearing.

<sup>b</sup> **Hormone-releasing** intrauterine devices and **hormonal** contraceptives are not considered an acceptable method in female study subjects due to potential induction of metabolism by VX-659; however, female subjects are not required to discontinue their use of hormone-releasing intrauterine devices or hormonal contraceptives.





**Additional notes:**

- If over the course of the study the subject meets the criteria for waiving the contraception requirements, the subject does not need to follow the contraceptive methods listed in [Table 11-3](#).
- Male subjects must not donate sperm during the period starting from the first dose of study drug until 90 days after the last dose of study drug.
- Female subjects should not nurse a child during the period starting from the first dose of study drug until 90 days after the last dose of study drug.
- For male subjects with a female partner of childbearing potential, the couple should not plan to become pregnant during the study or within 90 days after the last dose of study drug, with the exception of couples who plan to become pregnant by artificial insemination using sperm banked by the male subject before the first dose of study drug or sperm from another source.

**11.7.7.2 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 female subject becomes pregnant during study participation, 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. Male subjects with female partners who become pregnant during the study must use a male condom to avoid exposure of a potential embryo or fetus to study drug via the seminal fluid.

If confirmed to be on active drug, 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**

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

**12.1 Sample Size and Power**

Approximately 360 subjects will be enrolled and randomized (1:1) to the VX-659/TEZ/IVA arm or the triple placebo arm. This sample size was determined to provide adequate power for the key secondary endpoint of number of PEx through Week 24. Information regarding the powering of primary and key secondary endpoints is provided below.

**Power for Primary Efficacy Endpoint**

The primary efficacy endpoint is the absolute change in ppFEV<sub>1</sub> from baseline at Week 4. The primary null hypothesis to be tested is that the mean absolute change in ppFEV<sub>1</sub> from baseline is the same for the 2 treatment groups, VX-659/TEZ/IVA and placebo. If the number of subjects

included in the IA is 140, the null hypothesis will be tested at a 2-sided significance level of 0.044 during the IA and at an overall 2-sided significance level of 0.05.

Assuming a within-group SD of 7 percentage points and a 5% dropout rate at Week 4, an IA sample size of 70 subjects in each treatment group will have approximately 98% power to detect a difference between the treatment groups of 5.0 percentage points for the mean absolute change in ppFEV<sub>1</sub> from baseline at Week 4, based on a 2-sided, 2-sample *t*-test at a significance level of 0.044. If the *P* value fails to cross the efficacy boundary during the IA (*P* value  $\geq 0.044$ ; assuming 140 subjects included in the IA), the primary endpoint of absolute change in ppFEV<sub>1</sub> from baseline at Week 4 will be tested after all subjects complete study participation at an alpha of 0.01. A final analysis sample size of 180 subjects in each treatment group will have approximately 99% power to detect a difference between the treatment groups of 5.0 percentage points for the mean absolute change in ppFEV<sub>1</sub> from baseline at Week 4, based on a 2-sided, 2-sample *t*-test at a significance level of 0.01. All power calculations were based on EAST software Version 6.4.

### Power for Selected Key Secondary Endpoints

A key secondary endpoint is the absolute change in ppFEV<sub>1</sub> from baseline through Week 24. Assuming a within-group SD of 7 percentage points and a 10% dropout rate at Week 24, a sample size of 180 subjects in each treatment group will have approximately 99% power to detect a difference between the treatment groups of 5.0 percentage points for the absolute change in ppFEV<sub>1</sub> from baseline through Week 24, based on a 2-sided, 2-sample *t*-test at a significance level of 0.05.

Another key secondary endpoint is the number of PEx through Week 24. Assuming a rate of PEx for the placebo group of 0.6 over 24 weeks and a 10% dropout rate, with 180 subjects and the overdispersion parameter of 0.5 in each treatment group, the power to detect a 40% reduction in the PEx rate for TC group compared to placebo group is approximately 80%, based on a 2-sided, 2-sample negative binomial regression model test for the ratio of rates, at a significance level of 0.05.

## 12.2 Analysis Sets

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

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

The **FAS** will include all randomized subjects who carry the intended *CFTR* allele mutation and receive at least 1 dose of study drug. The FAS will be used to summarize subject demographics and baseline characteristics, and for all efficacy analyses in which subjects will be analyzed according to their randomized treatment group, unless otherwise specified.

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

Additional analysis sets related to the interim analysis will be described in the SAP.

## 12.3 Statistical Analysis

### 12.3.1 General Considerations

**Continuous variables** will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, median, minimum value (min), and maximum value (max). The precision of the measurement for each continuous variable will be specified in the SAP. Unless otherwise specified, min and max values will be reported with the same precision as the units of the raw data. The mean, median, and SD will be reported to 1 additional decimal place. Any values that require a transformation to standard units (metric or SI) will be converted with the appropriate precision.

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

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

**Absolute change** from baseline will be calculated as post-baseline value – baseline value.

The **Treatment-emergent (TE) Period** will include the time from the first dose of study drug in the Treatment Period (TC or Placebo) to 28 days after the last dose of the study drug or to the completion of study participation date (as defined in [Section 9.1.6](#)), whichever occurs first.

### 12.3.2 Background Characteristics

#### 12.3.2.1 Subject Disposition

The number and percentage of subjects in each disposition category (e.g., randomized, included in the FAS, included in the Safety Set, completed Treatment Period, completed study, prematurely discontinued treatment or study with a breakdown of the reasons for discontinuation, and entered an open-label study) will be summarized overall and by treatment group.

#### 12.3.2.2 Demographics and Baseline Characteristics

Demographic, medical history, and baseline characteristics will be summarized using descriptive summary statistics.

The following demographics and baseline characteristics will be summarized overall and by treatment group for the FAS and will include (but are not limited to): sex, race, baseline age, baseline weight, baseline height, baseline BMI, baseline ppFEV<sub>1</sub>, and baseline SwCl.

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

No statistical tests will be performed to evaluate baseline imbalance between treatment groups.

#### 12.3.2.3 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug-Dictionary and categorized as follows:

- **Prior medication:** any medication that was administered during the 56 days before initial dosing of study drug
- **Concomitant medication:** medication continued or newly received during the TE Period
- **Post-treatment medication:** medication continued or newly received after the TE Period

A given medication may be classified as a prior medication, a concomitant medication, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment. If a medication has a missing or partially missing start/end date or time and if it cannot be determined whether it was taken before the first dose of study drug, concomitantly during the TE Period, or after the TE Period, it will be considered in all 3 categories of prior, concomitant, and post-treatment medication.

Prior medications and concomitant medications will be summarized descriptively by Preferred Name based on the FAS. Post-treatment medications will be provided separately in an individual subject data listing.

#### **12.3.2.4 Study Drug Exposure and Compliance**

Study drug exposure will be summarized overall and by treatment group, based on the Safety Set in terms of the duration of treatment a subject received (in days), defined as the last day – the first day of study drug plus 1, regardless of study drug interruption.

Study drug compliance will be summarized overall and by treatment group based on the FAS, and will be calculated as:  $100 \times [1 - (\text{total number of days of study drug interruption}) / (\text{duration of study drug exposure in days})]$ . A study drug interruption on a given day is defined as an interruption of any study drug on that day.

In addition, percentage of tablets taken will also be summarized overall and by treatment group based on the FAS, and will be calculated as  $100 \times [(\text{total number of tablets dispensed}) - (\text{total number of tablets returned})] / (\text{total number of tablets planned to be taken per day} \times \text{duration of study drug exposure in days})$ .

#### **12.3.2.5 Important Protocol Deviations**

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. The rules for identifying an IPD will be described in the SAP.

All IPDs will be provided in an individual subject data listing, and summarized, as appropriate.

### **12.3.3 Efficacy and Pharmacodynamic Analysis**

The primary objective of the study is the evaluation of the efficacy of VX-659 in TC with TEZ and IVA. The analyses described in this section will be based on the FAS, unless otherwise specified.

#### **12.3.3.1 Final Analysis**

##### **12.3.3.1.1 Analysis of Primary Variables**

The primary efficacy variable is the absolute change in ppFEV<sub>1</sub> from baseline at Week 4. The analysis of this variable will be performed using a mixed-effects model for repeated measures (MMRM) with change from baseline at Day 15, Week 4, Week 8, Week 12, Week 16, and

Week 24 as the dependent variable. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects, with continuous baseline ppFEV<sub>1</sub>, age at screening (<18 versus ≥18 years of age) and sex (male versus female) as covariates. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the *F*-test for fixed effects will be estimated using the Kenward-Roger approximation. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, a compound symmetry covariance structure will be used instead. Conditional on the observed data and covariates, missing data will be assumed to be missing at random; consequently, no imputation of missing data will be performed.

The primary result obtained from the model will be the estimated treatment difference at Week 4. The adjusted mean difference at Week 4 with 2-sided 95% confidence intervals and 2-sided *P* values will be provided. Furthermore, the adjusted mean and treatment difference at each post-baseline visit will also be provided, obtained from the model.

### 12.3.3.1.2 Analysis of Secondary Variables

#### Analysis of Key Secondary Variables

The key secondary efficacy variables include:

- **Absolute change in ppFEV<sub>1</sub> through Week 24:** Analysis of this variable will be based on an MMRM model that is exactly the same as the primary efficacy variable. Data obtained from the Day 15, Week 4, Week 8, Week 12, Week 16, and Week 24 Visits will be included in the model, however, the Day 15 Visit will not be included in the estimation of the average treatment effect through Week 24.
- **Number of PEx through Week 24:** Analysis of this variable will be performed using a negative binomial regression model with a fixed effect for treatment, as well as continuous baseline ppFEV<sub>1</sub>, age at screening (<18 versus ≥18 years of age), and sex (male versus female) as covariates. The logarithm of the subject-specific PEx analysis period duration (defined in the SAP) will be treated as the offset in the model.
- **Absolute change in SwCI from baseline through Week 24:** Analysis of this PD variable will be based on an MMRM model similar to the analysis of the primary efficacy variable. Data obtained from Week 4, Week 8, Week 12, and Week 24 Visits will be included in the model and all of these visits will be included in the estimation of the average treatment effect through Week 24.
- **Absolute change in the CFQ-R respiratory domain score from baseline through Week 24:** Analysis of this domain will be based on an MMRM model similar to the analysis of the primary efficacy variable. Data obtained from Week 4, Week 8, Week 12, Week 16, and Week 24 Visits will be included in the model and all of these visits will be included in the estimation of the average treatment effect through Week 24.
- **Absolute change in BMI from baseline at Week 24:** Analysis of this variable will be based on an MMRM model similar to the analysis of the primary efficacy variables. Data obtained

from Day 15, Week 4, Week 8, Week 12, Week 16, and Week 24 Visits will be included in the model.

- **Absolute change in SwCI from baseline at Week 4:** Analysis of this variable will be based on an MMRM similar to the analysis of the primary efficacy variable. Data obtained from Week 4, Week 8, Week 12, and Week 24 Visits will be included in the model to estimate the treatment effect at Week 4.
- **Absolute change in CFQ-R respiratory domain score from baseline at Week 4:** Analysis of this variable will be based on an MMRM model similar to the analysis of the primary efficacy variable. Data obtained from the Week 4, Week 8, Week 12, and Week 24 Visits will be included in the model to estimate the treatment effect at Week 4.

The key secondary endpoints will be formally tested only during the final analysis when all subjects have completed study participation and the primary endpoint is statistically significant either at the IA or at the final analysis. Additional details will be provided in the SAP.

### **Analysis of Other Secondary Variables**

Other secondary efficacy variables include:

- **Time-to-first PEx through Week 24:** Time-to-first PEx will be analyzed using the Cox regression model. The model will include a fixed effect for treatment, as well as continuous baseline ppFEV<sub>1</sub>, age at screening (<18 versus ≥18 years of age), and sex (male versus female) as covariates. A subject who does not experience a PEx during the PEx analysis period will be censored at the PEx analysis period end date. If the proportional hazards assumption is violated for any of the categorical covariates, a stratified Cox regression will be conducted. Additionally, the Kaplan-Meier method will be used to produce a graphical presentation of the cumulative exacerbation-free survival rate for each treatment group and to estimate the cumulative exacerbation-free survival rate by treatment group. Note: If the number of events is <5 in either treatment group, Cox regression will not be performed and the analysis of the time-to-first event will be restricted to the Kaplan-Meier method.
- **Absolute change in BMI z-score from baseline at Week 24 (for subjects ≤20 years of age at Baseline):** Analysis of this variable will be based on an MMRM model similar to the analysis of the primary efficacy variable, for subjects ≤20 years of age at Baseline. Data obtained from Day 15, Week 4, Week 8, Week 12, Week 16, and Week 24 Visits will be included in the model.
- **Absolute change in body weight from baseline at Week 24:** Analysis of this variable will be based on an MMRM model similar to the analysis of the primary efficacy variable. Data obtained from Day 15, Week 4, Week 8, Week 12, Week 16, and Week 24 Visits will be included in the model.

Additional details will be provided in the SAP.

### 12.3.3.3 Interim Analysis

#### 12.3.3.3.1 Analysis of Primary Variables

During the IA, the analysis of the primary efficacy variable of absolute change in ppFEV<sub>1</sub> from baseline at Week 4 will be performed using an MMRM with change from baseline at Day 15 and Week 4 as the dependent variable. Other details of the model are same as that described for the final analysis (Section 12.3.3.1.1).

#### 12.3.3.3.2 Analysis of Key Secondary Variables

The following key secondary efficacy and pharmacodynamic variables will be analyzed during the IA using an Analysis of Covariance (ANCOVA) model and nominal *P* value will be provided for descriptive purpose:

1. Absolute change in SwCl from baseline at Week 4
2. Absolute change in CFQ-R respiratory domain score from baseline at Week 4

The model will use the change from baseline value at Week 4 as the dependent variable and include treatment group as fixed effects with continuous baseline ppFEV<sub>1</sub>, age at screening (<18 versus ≥18 years of age), and sex (male versus female) as covariates.

Additional details will be provided in the SAP.

#### 12.3.3.4 Multiplicity Adjustment

The Lan and DeMets alpha spending function will be applied to the primary endpoint of the absolute change in ppFEV<sub>1</sub> at Week 4 to control the overall type I error rate of 0.05 such that an alpha of 0.01 will be preserved for the final analysis.<sup>21</sup>

If the number of subjects included in the IA is 140, the primary endpoint of the absolute change from baseline in ppFEV<sub>1</sub> at Week 4 will be tested at an alpha of 0.044 during the IA. The actual alpha at the IA ( $\alpha_0$ ) will be determined based on the actual number of subjects included in the IA. If the study does not cross the efficacy boundary during the IA (*P* value  $\geq \alpha_0$ ), then the primary endpoint will be tested at an alpha of 0.01 at the final analysis when all subjects complete study participation.

The key secondary endpoints will be formally tested at an alpha of 0.05 at the final analysis when all subjects complete study participation only if the primary endpoint is statistically significant at the IA or at the final analysis. A hierarchical testing procedure will be used to control the type I error rate for the multiple key secondary endpoints tested at an alpha of 0.05. For a test at any step to be considered statistically significant within the testing hierarchy, it must be statistically significant, and all previous tests (if any) within the hierarchy must be statistically significant at the 0.05 level. The testing order of the key secondary endpoints is as follows:

1. First key secondary endpoint: Absolute change in ppFEV<sub>1</sub> from baseline through Week 24
2. Second key secondary endpoint: Number of PEx through Week 24

3. Third key secondary endpoint: Absolute change in SwCl from baseline through Week 24
4. Fourth key secondary endpoint: Absolute change in CFQ-R respiratory domain from baseline through Week 24
5. Fifth key secondary endpoint: Absolute change in BMI from baseline at Week 24
6. Sixth key secondary endpoint: Absolute change in SwCl from baseline at Week 4
7. Seventh key secondary endpoint: Absolute change in CFQ-R respiratory domain score from baseline at Week 4

### 12.3.4 Safety Analysis

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

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

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

All safety data from the TE Period will be summarized by treatment group.

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

#### 12.3.4.1 Adverse Events

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

- **Pretreatment AE:** any AE that occurred before the first dose date of study drug
- **TEAE:** any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug through the end of the TE Period
- **Post-treatment AE:** any AE that worsened (either in severity or seriousness) or that was newly developed after the TE Period

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

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



- TEAEs leading to treatment interruption
- Serious TEAEs
- TEAEs leading to death
- Grade 3 and Grade 4 TEAEs
- Frequently reported TEAEs

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 in the relationship summaries.

In addition, a listing containing individual subject level AE data for all deaths and other serious and significant AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

#### **12.3.4.2 Clinical Laboratory Assessments**

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

The number and percentage of subjects with at least 1 threshold analysis event during the TE Period will be summarized overall and by treatment group. The threshold analysis criterion shift from baseline will also be summarized for select laboratory parameters. The threshold analysis criteria and the parameter selection criteria will be provided in the SAP.

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

#### **12.3.4.3 Electrocardiogram**

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

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

Additional ECG analyses may be described in the SAP.

#### **12.3.4.4 Vital Signs**

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized by treatment group at each visit. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute).

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

Additional vital signs analyses may be described in the SAP.

#### **12.3.4.5 Pulse Oximetry**

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

The number and percentage of subjects with shift changes from baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the TE Period will be summarized overall and by treatment group.

#### **12.3.4.6 Physical Examination**

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

#### **12.3.4.7 Other Safety Analyses**

Details of other safety analyses will be included in the SAP.

### **12.3.6 Interim and IDMC Analyses**

#### **12.3.6.1 Interim Analyses**

An IA is planned when at least 140 subjects complete the Week 4 Visit and at least 100 subjects complete the Week 12 Visit. The IA will be performed by an external independent biostatistician who is not involved in and will not influence the conduct of the study, and the results will be reviewed by the IDMC. If the  $P$  value for the primary endpoint at the IA is less than  $\alpha_0$ , then the efficacy boundary has been crossed. Refer to [Section 12.3.3.4](#) for how  $\alpha_0$  is determined. If the IDMC declares that the study has crossed the efficacy boundary, then the study may be unblinded to a limited Vertex team to prepare a regulatory submission(s). Members of the limited Vertex unblinded team will not be involved in or influence the conduct of the remaining part of the study to protect the integrity of the study. The study will continue to completion and remain double-blinded through Week 24.

If the study does not cross the efficacy boundary (i.e., the  $P$  value for the primary endpoint at the IA is  $\geq \alpha_0$ ), the primary endpoint of the absolute change in ppFEV<sub>1</sub> from baseline at Week 4 will be tested after all subjects complete study participation at an alpha of 0.01.

The key secondary endpoints will be formally tested only during the final analysis when all subjects have completed study participation and the primary endpoint is statistically significant either at the IA or at the final analysis. The selected key secondary endpoints at Week 4 ([Section 12.3.3.1.2](#)) will be analyzed during the IA and nominal *P* value will be provided for descriptive purposes.

### **12.3.6.2 IDMC Analysis**

The IDMC ([Section 9.1.7](#)) will conduct periodic planned safety review(s) of study data and the planned efficacy IA. Details of the safety and efficacy review(s) will be described in the IDMC charter.

## **12.4 Clinical Pharmacology Analysis**

### **12.4.1 Pharmacokinetic Analysis**

The PK analysis of VX-659, TEZ, and IVA may be performed using nonlinear mixed effects modeling and/or standard noncompartmental analysis, as data allow. Metabolites, including M1-TEZ, may be included in the analyses as supported by data. Descriptive statistics will be used to summarize PK parameter values for all analytes.

A detailed description of the planned PK analysis will be presented in the CPAP.

### **12.4.2 Pharmacokinetic/Pharmacodynamic Analyses**

PD assessments to be included in PK/PD analyses may include SwCl, ppFEV<sub>1</sub>, as well as other endpoints such as BMI, BMI z-score, or CFQ-R respiratory domain score.

A sequential approach will be used to perform the population PK/PD analysis. The Bayesian estimates of individual PK parameters from the final population PK model will be used to simulate PK profiles for each subject. The simulated VX-659, TEZ, IVA, or metabolite plasma concentrations will be used in the potential pharmacological response models to describe changes in each endpoint from baseline. Fixed- and random-effect parameter estimates and the associated asymptotic SEs will be estimated. Descriptive statistics will be used to summarize Bayesian estimates of individual PK/PD parameters obtained from the population PK/PD model.

## **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 the ICF is signed until the subject completes study participation, as defined in [Section 9.1.6](#).

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](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm) (Accessed 28 September 2017). AEs of CTCAE Grades 4 and 5 will be documented as “life-threatening.” In considering the severity of an AE in a pediatric subject, the investigator will consider that reference ranges for pediatric clinical laboratory parameters may differ from those given in the CTCAE. The severity of an AE that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

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

Classification	Definition
<b>Mild (Grade 1)</b>	Mild level of discomfort and does not interfere with regular activities
<b>Moderate (Grade 2)</b>	Moderate level of discomfort and significantly interferes with regular activities
<b>Severe (Grade 3)</b>	Significant level of discomfort and prevents regular activities
<b>Life-threatening (Grade 4)</b>	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
<b>Related</b>	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.
<b>Possibly related</b>	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.
<b>Unlikely related</b>	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
<b>Not related</b>	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
<b>Dose not changed</b>	Study drug dose not changed in response to an AE
<b>Dose reduced</b>	Study drug dose reduced in response to an AE
<b>Drug interrupted</b>	Study drug administration interrupted in response to an AE
<b>Drug withdrawn</b>	Study drug administration permanently discontinued in response to an AE

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

<b>Classification</b>	<b>Definition</b>
<b>Not applicable</b>	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**

<b>Classification</b>	<b>Definition</b>
<b>Recovered/resolved</b>	Resolution of an AE with no residual signs or symptoms
<b>Recovered/resolved with sequelae</b>	Resolution of an AE with residual signs or symptoms
<b>Not recovered/not resolved (continuing)</b>	Either incomplete improvement or no improvement of an AE, such that it remains ongoing
<b>Fatal</b>	Outcome of an AE is death. “Fatal” will be used when death is at least possibly related to the AE.
<b>Unknown</b>	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 through completion of study participation, regardless of causality, will be reported by the investigator to Vertex GPS. In addition, all SAEs that occur after completion of study participation and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours**.

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

#### **13.1.2.3 Reporting Serious Adverse Events**

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

Please send completed SAE Forms to Vertex GPS via:

Email: [REDACTED] (preferred choice)

Fax: [REDACTED]

For questions, contact telephone: [REDACTED]

#### **13.1.2.4 Expedited Reporting and Investigator Safety Letters**

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

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

### **13.2 Administrative Requirements**

#### **13.2.1 Ethical Considerations**

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

#### **13.2.2 Subject Information and Informed Consent**

After the study has been fully explained, written informed consent will be obtained from the subject or legal representative or guardian (if applicable), and assent will be obtained from the subject (if applicable), before study participation. The method of obtaining and documenting the informed consent and assent (if applicable) and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by Vertex or its designee. When determining the age of the subject, other study eligibility criteria, and timing of collection applicable assessments, the informed consent will be used as the reference (e.g., age at time of informed consent, date of informed consent, timing of AE collection).

#### **13.2.3 Investigator Compliance**

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

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



#### **13.2.4 Access to Records**

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

#### **13.2.5 Subject Privacy**

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

For sites participating in the study in the US, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated regulations, 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, for subjects who have been lost to follow-up, the last contact, whichever occurs later, for the latest completing 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 CRFs/SAE Forms for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

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

Protocol deviations will be monitored and identified throughout study conduct as outlined in the Protocol Deviation Plan.

### **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

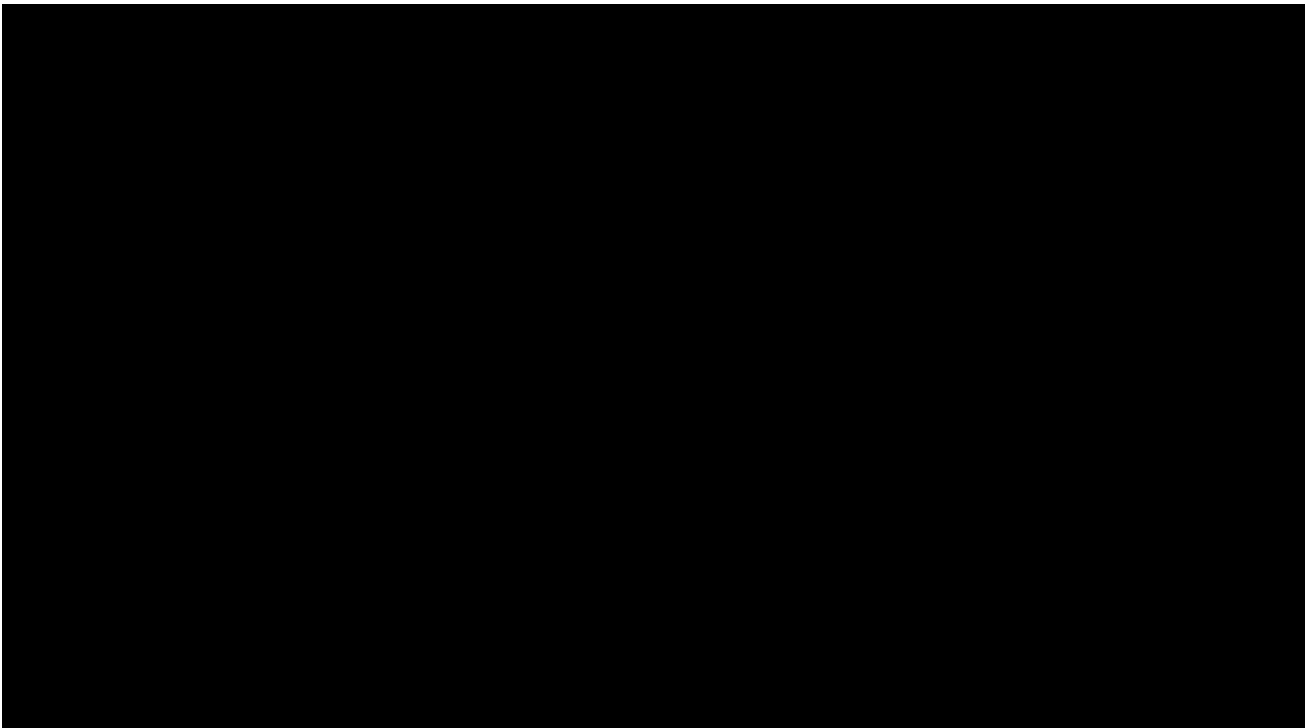
the study and will document the dates and details of study procedures, AEs, other observations, and subject status.

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 or other electronic media will be placed in the investigator's study file.

### **13.6 Publications and Clinical Study Report**



#### **13.6.2 Clinical Study Report**

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

## 14 REFERENCES

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## **APPENDIX A Eligible MF *CFTR* Mutations**

“MF” mutations are a subset of minimal function mutations that are non-responsive to TEZ, IVA, or TEZ/IVA. A mutation is considered an MF mutation if it meets at least 1 of the following 2 criteria:

- (1) biological plausibility of no translated protein (genetic sequence predicts the complete absence of CFTR protein), or
- (2) in vitro testing that supports lack of responsiveness to TEZ, IVA, or TEZ/IVA, and evidence of clinical severity on a population basis (as reported in large patient registries).

### **Inclusion of MF Mutations Based on In Vitro Testing**

Mutations that were considered to be MF mutations based on in vitro testing met the following criteria in in vitro experiments:

- baseline chloride transport that was <10% of wildtype CFTR
- an increase in chloride transport of <10% over baseline following the addition of TEZ, IVA, or TEZ/IVA in the assay

These mutations also had evidence of clinical severity on a population basis (per CFTR2 patient registry; accessed on 15 February 2016). Patients with these mutations on one allele and *F508del* on the other allele exhibited evidence of clinical severity as defined as:

- average sweat chloride >86 mmol/L, and
- prevalence of pancreatic insufficiency (PI) >50%

These clinical severity criteria do not apply to the individual subjects to be enrolled in the study, but were used to categorize each mutation on a population level.

### **Eligible MF Mutations**

The list below represents acceptable mutations, which are detectable by an FDA-cleared genotyping assay or other method (e.g., sequencing); however, this list may not include every eligible mutation, and investigators should contact the medical monitor regarding other mutations that may also meet study eligibility criteria.

**CFTR Mutations Eligible for VX17-659-102**

<b>MF Mutation Category</b>	<b>Mutation</b>					
Nonsense mutations	Q2X	L218X	Q525X	R792X	E1104X	
	S4X	Q220X	G542X	E822X	W1145X	
	W19X	Y275X	G550X	W882X	R1158X	
	G27X	C276X	Q552X	W846X	R1162X	
	Q39X	Q290X	R553X	Y849X	S1196X	
	W57X	G330X	E585X	R851X	W1204X	
	E60X	W401X	G673X	Q890X	L1254X	
	R75X	Q414X	Q685X	S912X	S1255X	
	L88X	S434X	R709X	Y913X	W1282X	
	E92X	S466X	K710X	Q1042X	Q1313X	
	Q98X	S489X	Q715X	W1089X	Q1330X	
	Y122X	Q493X	L732X	Y1092X	E1371X	
	E193X	W496X	R764X	W1098X	Q1382X	
	W216X	C524X	R785X	R1102X	Q1411X	
	Canonical splice mutations	185+1G→T	711+5G→A	1717-8G→A	2622+1G→A	3121-1G→A
		296+1G→A	712-1G→T	1717-1G→A	2790-1G→C	3500-2A→G
296+1G→T		1248+1G→A	1811+1G→C	3040G→C	3600+2insT	
405+1G→A		1249-1G→A	1811+1.6kbA→G	(G970R)	3850-1G→A	
405+3A→C		1341+1G→A	1811+1643G→T	3120G→A	4005+1G→A	
406-1G→A		1525-2A→G	1812-1G→A	3120+1G→A	4374+1G→T	
621+1G→T		1525-1G→A	1898+1G→A	3121-2A→G		
711+1G→T			1898+1G→C			
Small (≤3 nucleotide) insertion/deletion (ins/del) frameshift mutations	182delT	1078delT	1677delTA	2711delT	3737delA	
	306insA	1119delA	1782delA	2732insA	3791delC	
	306delTAGA	1138insG	1824delA	2869insG	3821delT	
	365-366insT	1154insTC	1833delT	2896insAG	3876delA	
	394delTT	1161delC	2043delG	2942insT	3878delG	
	442delA	1213delT	2143delT	2957delT	3905insT	
	444delA	1259insA	2183AA→G <sup>a</sup>	3007delG	4016insT	
	457TAT→G	1288insTA	2184delA	3028delA	4021dupT	
	541delC	1343delG	2184insA	3171delC	4022insT	
	574delA	1471delA	2307insA	3171insC	4040delA	
	663delT	1497delGG	2347delG	3271delGG	4279insA	
	849delG	1548delG	2585delT	3349insT	4326delTC	
	935delA	1609del CA	2594delGT	3659delC		
Non-small (>3 nucleotide) insertion/deletion (ins/del) frameshift mutations	CFTRdele1	CFTRdele16-17b	1461ins4			
	CFTRdele2	CFTRdele17a,17b	1924del7			
	CFTRdele2,3	CFTRdele17a-18	2055del9→A			
	CFTRdele2-4	CFTRdele19	2105-2117del13insAGAAA			
	CFTRdele3-10,14b-16	CFTRdele19-21	2372del8			
	CFTRdele4-7	CFTRdele21	2721del11			
	CFTRdele4-11	CFTRdele22-24	2991del32			
	CFTR50kdel	CFTRdele22,23	3121-977_3499+248del2515			
	CFTRdup6b-10	124del23bp	3667ins4			
	CFTRdele11	602del14	4010del4			
	CFTRdele13,14a	852del22	4209TGTT→AA			
CFTRdele14b-17b	991del5					

**CFTR Mutations Eligible for VX17-659-102**

<b>MF Mutation Category</b>	<b>Mutation</b>			
Missense mutations that	A46D <sup>b</sup>	V520F	Y569D <sup>b</sup>	N1303K
• Are not responsive in vitro to TEZ, IVA, or TEZ/IVA	G85E	A559T <sup>b</sup>	L1065P	
	R347P	R560T	R1066C	
<b>and</b>	L467P <sup>b</sup>	R560S	L1077P <sup>b</sup>	
• %PI>50% and SwCl <sup>-</sup> >86 mmol/L	I507del	A561E	M1101K	

CFTR: cystic fibrosis transmembrane conductance regulator; IVA: ivacaftor; SwCl: sweat chloride; TEZ: tezacaftor  
 Source: CFTR2.org [Internet]. Baltimore (MD): Clinical and functional translation of CFTR. The Clinical and Functional Translation of CFTR (CFTR2), US Cystic Fibrosis Foundation, Johns Hopkins University, the Hospital for Sick Children. Available at: <http://www.cftr2.org/>. Accessed 15 February 2016.

Notes: %PI: percentage of *F508del-CFTR* heterozygous patients in the CFTR2 patient registry who are pancreatic insufficient; SwCl: mean sweat chloride of *F508del-CFTR* heterozygous patients in the CFTR2 patient registry.

<sup>a</sup> Also known as 2183delAA→G.

<sup>b</sup> Unpublished data.



## 15            **PROTOCOL SIGNATURE PAGES**

### 15.1           **Sponsor Signature Page**

Protocol #:	VX17-659-102	Version #:	3.0	Version Date:	27 April 2018
Study Title: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-659 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the <i>F508del</i> Mutation and a Minimal Function Mutation (F/MF)					

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



**15.2 Investigator Signature Page**

Protocol #:	VX17-659-102	Version #:	3.0	Version Date:	27 April 2018
Study Title: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-659 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the <i>F508del</i> Mutation and a Minimal Function Mutation (F/MF)					

I have read Protocol VX17-659-102, Version 3.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-659, tezacaftor, and ivacaftor and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

\_\_\_\_\_  
Printed Name

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

