1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445/TEZ/IVA Combination Therapy in Subjects With Cystic Fibrosis Who Are 6 Years of Age and Older

Vertex Study Number: VX19-445-107

VX-445 IND Number: 132547

EudraCT Number: 2019-001827-11

Date of Protocol: 10 June 2021 (Version 2.0)

Replaces Version 1.0, dated 07 June 2019

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Summary of Changes to the Protocol

The previous version of this protocol (Version 1.0, 07 June 2019) was amended to create the current version (Version 2.0, 10 June 2021). The protocol history is provided below.

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.0, 07 June 2019	Original version
Version 2.0, 10 June 2021	Current version, updated to extend treatment period.

Key changes in the current version of the protocol are summarized below.

Change and Rationale	**Affected Sections**
Extended treatment from 96 weeks to 192 weeks (by adding Part B of 96-weeks treatment duration) to evaluate the longer-term safety and efficacy of VX-445/TEZ/IVA	Global; Section 2 (Synopsis: Study Duration, Study Design) and Sections 3, 8.2, 9.1, 9.1.1, 9.1.2, 9.4.1, and 12
Updated monitoring text to include flexibility for remote monitoring, as allowed by local regulations	Section 13.4

Typographical and administrative changes were also made to improve the clarity of the document.

2 PROTOCOL SYNOPSIS

Title A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445/TEZ/IVA Combination Therapy in Subjects With Cystic Fibrosis Who Are 6 Years of Age and Older

Brief Title Evaluation of Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are 6 Years of Age and Older

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

Objectives

Primary Objective

To evaluate the long-term safety and tolerability of VX-445/tezacaftor (TEZ)/ivacaftor (IVA) in subjects with cystic fibrosis (CF) who are 6 years of age and older

Secondary Objective

To evaluate the long-term efficacy and pharmacodynamics (PD) of VX-445/TEZ/IVA

Endpoints

Primary Endpoint

Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, pulse oximetry, and ophthalmologic examinations

Secondary Endpoints

- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$)
- Absolute change in sweat chloride (SwCl)
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain (RD) score
- Absolute change in body mass index (BMI) and BMI-for-age z-score
- Number of pulmonary exacerbations (PEx) and CF-related hospitalizations
- Absolute change in lung clearance $index_{2.5}$ ($LCI_{2.5}$)
- Absolute change in weight and weight-for-age z-score
- Absolute change in height and height-for-age z-score

Other Endpoints

- Absolute change in fecal elastase-1 (FE-1) levels
- Absolute change in serum levels of immunoreactive trypsinogen (IRT)

Number of Subjects Subjects who participate in parent study VX18-445-106 Part B and meet eligibility criteria are eligible to enroll. Approximately 56 subjects are expected to enroll in this study.

Study Population Male and female subjects with CF who are 6 years of age and older who are homozygous for the *F508del* mutation or heterozygous for *F508del* and a minimal function mutation.

Investigational Drug Study drug refers to VX-445/TEZ/IVA and IVA.

Study drugs will be orally administered as 2 fixed-dose combination film-coated tablets (VX-445/TEZ/IVA) in the morning and as 1 film-coated tablet (IVA) in the evening.

Active substance: VX-445/TEZ (VX-661)/IVA (VX-770)

Activity: CFTR corrector, CFTR corrector, and CFTR potentiator

Strength:

- 100 mg VX-445/50 mg TEZ/75 mg IVA
- 50 mg VX-445/25 mg TEZ/37.5 mg IVA

Active substance: IVA (VX-770)

Activity: CFTR potentiator

Strength:

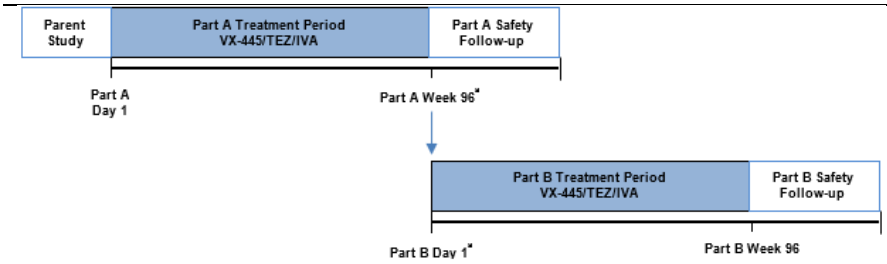
- 150 mg IVA
- 75 mg IVA

Study Duration For subjects who enroll in both Parts A and B, the total study duration is approximately 196 weeks from the Part A Day 1 Visit (96 weeks for the Part A Treatment Period, 96 weeks for the Part B Treatment Period, and 4 weeks for the Safety Follow-up Period).

Study Design This is a Phase 3, 2-part, multicenter, open-label extension safety study for subjects who completed the Treatment Period in the parent study (VX18-445-106 Part B) and meet eligibility criteria. The study design in shown in Figure 2-1.

Subjects who complete Part A will have the opportunity to enroll in Part B for an additional 96 weeks.

Figure 2-1 Schematic of the Study Design



IVA: ivacaftor; TEZ: tezacaftor

Note: The parent study is VX18-445-106 Part B, a Phase 3 study investigating VX-445/TEZ/IVA in subjects 6 through 11 years of age. The figure is not drawn to scale.

[a] Subjects whose Part B Day 1 Visit is on the same day or within 1 calendar day of the Part A Week 96 Visit do NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 96 Visit. Subjects whose Part B Day 1 Visit is more than 1 calendar day after the Part A Week 96 Visit must complete all assessments specified for the Part A Week 96 AND Part B Day 1 Visits.

All subjects will receive VX-445/TEZ/IVA at weight-appropriate dosage levels for 96 weeks in Part A. In Part B, subjects will receive VX-445/TEZ/IVA at age- and weight-appropriate dosage levels for 96 weeks (Table 2-1).

Table 2-1 Treatment Period Dosages

Subject Weight	VX-445 Dosage	TEZ Dosage	IVA Dosage
Part A, subjects ≥6 years of age			
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
<30 kg	100 mg qd	50 mg qd	75 mg q12h
Part B, subjects ≥6 to <12 years of age			
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
<30 kg	100 mg qd	50 mg qd	75 mg q12h
Part B, subjects ≥12 years of age			
All weights	200 mg qd	100 mg qd	150 mg q12h

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

Assessments

Safety: AEs, clinical laboratory assessments, ECGs, vital signs, pulse oximetry, ophthalmologic examinations, and physical examinations

Efficacy and PD: spirometry, SwCl, CFQ-R, weight, height, multiple breath washout, and documentation of other events related to outcome (e.g., PEx, CF-related hospitalizations)

Other Assessments:

FE-1 and IRT will be measured to assess exocrine pancreatic function.

Blood samples for blood biomarker analysis will be collected at select study visits for potential exploratory evaluation of correlations between blood biomarkers with PD, treatment benefit, and AEs.

Statistical Analyses

The primary objective of the study is the evaluation of the long-term safety and tolerability of VX-445/TEZ/IVA. The safety endpoints of long-term treatment include AEs, clinical laboratory values, ECGs, vital signs, pulse oximetry, and ophthalmologic examinations from the first dose of study drug in this study, for subjects who receive at least 1 dose of study drug in this long-term safety study. The safety analysis will be descriptive.

The secondary objective of the study is the evaluation of long-term efficacy and PD of VX-445/TEZ/IVA, as assessed by spirometry, SwCl, CFQ-R, PEx and CF-related hospitalizations, BMI, height, weight (and related z-scores), and $LCI_{2.5}$. Methods of efficacy analyses will be similar to those used in the parent study unless otherwise specified.

Interim Analyses

Interim analyses may take place at any time at the discretion of the sponsor.

IDMC Reviews

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

3 SCHEDULE OF ASSESSMENTS

Table 3-1 and Table 3-2 provide the schedules of assessments. All visits are to be scheduled relative to the Day 1 Visit in each Part.

The Cystic Fibrosis Questionnaire-Revised (CFQ-R) must be completed before any other assessment (except informed consent form [ICF] signing) at relevant clinic visits. Multiple breath washout (MBW) assessments should be performed before spirometry, and ECG should be performed before any assessments that may affect heart rate (such as blood draws). 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 VX19-445-107: Part A Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Part A Treatment Period (96 weeks)						Part A ETT Visit[b]	Part A Safety Follow-up Visit[c] (28 ± 7 Days After Last Dose of Study Drug)	Comments
	Day 1[d]	Weeks 8, 16, 24, 36 (± 5 Days)	Weeks 4, 12, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92 (± 5 Days)	Week 48 (± 5 Days)	Weeks 60, 72, 84 (± 5 Days)	Week 96[e] (± 5 Days)			
Clinic visit	X	X		X	X	X	X	X	
Telephone contact			X						When telephone contact takes the place of a clinic visit, a urine pregnancy test will be performed with a home kit provided by the study site (Section 11.5.2).
Informed consent and assent	X								
Inclusion and exclusion criteria confirmation	X								See Section 8 for details.
CFQ-R	X	Weeks 8, 24		X	Week 72	X	X	X	To be completed before any other assessments scheduled at relevant visits (Section 11.3.5).
Ophthalmologic examination				X		X	X		Subjects will have an ophthalmologic examination at Week 48 and at Week 96 (Section 11.5.5). In addition, an ophthalmologic examination will be performed at the ETT Visit for subjects who discontinue study drug if the subject has received at least 12 weeks of study drug since their last study ophthalmologic examination.
Full physical examination	X					X	X		Symptom-directed physical examinations will be performed at any time if deemed necessary by the investigator or healthcare provider (Section 11.5.3).
Weight, height, and BMI	X	X		X	X	X	X	X	Weight and height measured with shoes off (Section 11.3.4).

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

[b] If a subject prematurely discontinues study drug treatment, an ETT Visit should be scheduled as soon as possible after the decision to discontinue treatment (Section 9.1.3).

[c] The Safety Follow-up Visit is required for all subjects unless otherwise specified. 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 9.1.2).

[d] The Day 1 Visit should be on the same day as the last scheduled visit of the parent study (Section 9.1.1). Subjects whose Day 1 Visit is NOT within 1 day of the last scheduled visit of the parent study will repeat all Day 1 assessments. Subjects whose Day 1 Visit is within 1 day of the last scheduled visit of the parent study will NOT have to repeat any Day 1 assessments that were specified to be performed at the last scheduled visit in the parent study.

Table 3-1 Study VX19-445-107: Part A Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Part A Treatment Period (96 weeks)						Part A ETT Visit[b]	Part A Safety Follow-up Visit[c] (28 ± 7 Days After Last Dose of Study Drug)	Comments
	Day 1[d]	Weeks 8, 16, 24, 36 (± 5 Days)	Weeks 4, 12, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92 (± 5 Days)	Week 48 (± 5 Days)	Weeks 60, 72, 84 (± 5 Days)	Week 96[e] (± 5 Days)			
Vital signs	X	X		X	X	X	X	X	Performed after subject has been at rest (seated or supine) for at least 5 minutes (Section 11.5.3).
Pulse oximetry	X	X		X	X	X	X	X	Performed after subject has been at rest for at least 5 minutes (Section 11.5.3).
Standard 12-lead ECG	X	Week 24		X	Week 72	X	X	X	Performed after subject has been at rest for at least 5 minutes (Section 11.5.4).
Spirometry	X	X		X	X	X	X	X	Should be performed pre-bronchodilator at approximately the same time at each visit (Section 11.3.1).
Sweat chloride	X	Week 24		X	Week 72	X	X		At each time point, 2 samples will be collected (1 sample from each arm; Section 11.3.2).
Pregnancy test (all female subjects)	urine	urine	urine	urine	urine	serum	serum	serum	At telephone contact visits, a urine pregnancy test will be performed with a home kit provided by the study site (Section 11.5.2).
Serum chemistry	X	X		X	X	X	X	X	Section 11.5.2
Hematology	X	X		X	X	X	X	X	Section 11.5.2
Coagulation	X	Week 24		X	Week 72	X	X	X	Section 11.5.2
Urinalysis	X			X		X	X		Section 11.5.2
Multiple breath washout	X	Week 24		X	Week 72	X	X		Performed in multiple replicates, pre-bronchodilator, and before the spirometry assessment (Section 11.3.3).
Blood biomarker sample	X			X		X	X		Section 11.4.2

[e] Subjects whose Part B Day 1 Visit is on the same day or within 1 calendar day as the Part A Week 96 Visit do NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 96 Visit. Subjects whose Part B Day 1 Visit is more than 1 calendar day after the Part A Week 96 Visit must complete all assessments specified for the Part A Week 96 AND Part B Day 1 Visits.

Table 3-1 Study VX19-445-107: Part A Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Part A Treatment Period (96 weeks)						Part A ETT Visit[b]	Part A Safety Follow-up Visit[c] (28 ± 7 Days After Last Dose of Study Drug)	Comments
	Day 1[d]	Weeks 8, 16, 24, 36 (± 5 Days)	Weeks 4, 12, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92 (± 5 Days)	Week 48 (± 5 Days)	Weeks 60, 72, 84 (± 5 Days)	Week 96[e] (± 5 Days)			
FE-1	X	Week 24		X		X	X		Samples may be collected by the subject's caregiver up to 24 hours before the study visit (e.g., at home). The sample may be collected pre- or postdose (Section 11.4.1).
IRT	X	Week 24		X	Week 72	X	X		Section 11.4.1
Study drug dosing	Day 1 through evening before Week 96 Visit								Subjects on study drug interruption at the end of the parent study may not begin dosing until they meet the criteria in Section 9.8. Refer to Section 9.6.1 for study drug administration details.
Study drug count		X		X	X	X	X		
Other events related to outcome	Continuous from signing of ICF through completion of study participation								Includes PEx, administration of antibiotic therapy for sinopulmonary signs/symptoms, and hospitalizations for CF (Section 11.3.6). Completion of study participation is defined in Section 9.1.5.
Medications review	Continuous from signing of ICF through completion of study participation								Completion of study participation is defined in Section 9.1.5.
Treatment and procedures review	Continuous from signing of ICF through completion of study participation								Completion of study participation is defined in Section 9.1.5.
AEs and SAEs	Continuous from signing of ICF through completion of study participation								Completion of study participation is defined in Section 9.1.5.

AE: adverse event; BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; ETT: Early Termination of Treatment; FE-1: fecal elastase-1; ICF: informed consent form; IRT: immunoreactive trypsinogen; PEx: pulmonary exacerbation; SAE: serious adverse event

Table 3-2 Study VX19-445-107: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Part B Treatment Period (96 weeks)					Part B ETT Visit[b]	Part B Safety Follow-up Visit[c] (28 ± 7 Days After Last Dose of Study Drug)	Comments
	Day 1[d]	Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92 (± 5 Days)	Weeks 12, 36, 60, 84 (± 5 Days)	Weeks 24, 48, 72 (± 5 Days)	Week 96 (± 5 Days)			
Clinic visit	X		X	X	X	X	X	
Telephone contact		X						When telephone contact takes the place of a clinic visit, a urine pregnancy test will be performed with a home kit provided by the study site (Section 11.5.2).
Part B Informed consent and assent	X							
Inclusion and exclusion criteria confirmation	X							See Section 8 for details.
CFQ-R	X			X	X	X	X	To be completed before any other assessments scheduled at relevant visits (Section 11.3.5).
Ophthalmologic examination					X	X		Subjects will have an ophthalmologic examination at Week 96 (Section 11.5.5). In addition, an ophthalmologic examination will be performed at the ETT Visit for subjects who discontinue study drug if the subject has received at least 12 weeks of study drug since their last study ophthalmologic examination.
Full physical examination	X				X	X		Symptom-directed physical examinations will be performed at any time if deemed necessary by the investigator or healthcare provider (Section 11.5.3).
Weight, height, and BMI	X		X	X	X	X	X	Weight and height measured with shoes off (Section 11.3.4).
Vital signs	X		X	X	X	X	X	Performed after subject has been at rest (seated or supine) for at least 5 minutes (Section 11.5.3).

[a] All assessments will be performed before study drug dosing unless noted otherwise.
[b] If a subject prematurely discontinues study drug treatment, an ETT Visit should be scheduled as soon as possible after the decision to discontinue treatment (Section 9.1.3).
[c] The Safety Follow-up Visit is required for all subjects unless otherwise specified. 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 9.1.2).
[d] Subjects whose Part B Day 1 Visit is on the same day or within 1 calendar day as the Part A Week 96 Visit do NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 96 Visit. Subjects whose Part B Day 1 Visit is more than 1 calendar day after the Part A Week 96 Visit must complete all assessments specified for the Part A Week 96 AND Part B Day 1 Visits.

Table 3-2 Study VX19-445-107: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Part B Treatment Period (96 weeks)					Part B ETT Visit[b]	Part B Safety Follow-up Visit[c] (28 ± 7 Days After Last Dose of Study Drug)	Comments
	Day 1[d]	Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92 (± 5 Days)	Weeks 12, 36, 60, 84 (± 5 Days)	Weeks 24, 48, 72 (± 5 Days)	Week 96 (± 5 Days)			
Pulse oximetry	X		X	X	X	X	X	Performed after subject has been at rest for at least 5 minutes (Section 11.5.3).
Standard 12-lead ECG	X			X	X	X	X	Performed after subject has been at rest for at least 5 minutes (Section 11.5.4).
Spirometry	X		X	X	X	X	X	Should be performed pre-bronchodilator at approximately the same time at each visit (Section 11.3.1).
Sweat chloride	X			X	X	X		At each time point, 2 samples will be collected (1 sample from each arm; Section 11.3.2).
Pregnancy test (all female subjects)	urine	urine	urine	urine	serum	serum	serum	At telephone contact visits, a urine pregnancy test will be performed with a home kit provided by the study site (Section 11.5.2).
Serum chemistry	X		X	X	X	X	X	Section 11.5.2
Hematology	X		X	X	X	X	X	Section 11.5.2
Coagulation	X			X	X	X	X	Section 11.5.2
Urinalysis	X			Week 48	X	X		Section 11.5.2
Multiple breath washout	X			X	X	X		Performed in multiple replicates, pre-bronchodilator, and before the spirometry assessment (Section 11.3.3).
Blood biomarker sample	X			Week 48	X	X		Section 11.4.2
FE-1	X			Week 48	X	X		Samples may be collected by the subject's caregiver up to 24 hours before the study visit (e.g., at home). The sample may be collected pre- or postdose (Section 11.4.1).
IRT	X			X	X	X		Section 11.4.1

Table 3-2 Study VX19-445-107: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Part B Treatment Period (96 weeks)					Part B ETT Visit[b]	Part B Safety Follow-up Visit[c] (28 ± 7 Days After Last Dose of Study Drug)	Comments
	Day 1[d]	Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92 (± 5 Days)	Weeks 12, 36, 60, 84 (± 5 Days)	Weeks 24, 48, 72 (± 5 Days)	Week 96 (± 5 Days)			
Study drug dosing	Day 1 through evening before Week 96 Visit							Subjects on study drug interruption at the end of the parent study may not begin dosing until they meet the criteria in Section 9.8. Refer to Section 9.6.1 for study drug administration details.
Study drug count			X	X	X	X		
Other events related to outcome	Continuous from signing of ICF through completion of study participation							Includes PEx, administration of antibiotic therapy for sinopulmonary signs/symptoms, and hospitalizations for CF (Section 11.3.6). Completion of study participation is defined in Section 9.1.5.
Medications review	Continuous from signing of ICF through completion of study participation							Completion of study participation is defined in Section 9.1.5.
Treatment and procedures review	Continuous from signing of ICF through completion of study participation							Completion of study participation is defined in Section 9.1.5.
AEs and SAEs	Continuous from signing of ICF through completion of study participation							Completion of study participation is defined in Section 9.1.5.

AE: adverse event; BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; ETT: Early Termination of Treatment; FE-1: fecal elastase-1; ICF: informed consent form; IRT: immunoreactive trypsinogen; PEx: pulmonary exacerbation; SAE: serious adverse event

4 TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ECG	electrocardiogram
EDC	electronic data capture
ETT	Early Termination of Treatment
EU	European Union
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FDA	Food and Drug Administration
FDC	fixed-dose combination
FE-1	fecal elastase-1
$FEF_{25\%-75\%}$	forced expiratory flow, midexpiratory phase
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GLI	Global Lung Function Initiative
GPS	Global Patient Safety
HBE	human bronchial epithelial (cells)
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	Investigational New Drug (application) (US)
IPD	important protocol deviation
IRB	institutional review board
IRT	immunoreactive trypsinogen
IV	intravenous
IVA	ivacaftor
IWRS	interactive web response system
LCI	lung clearance index
$LCI_{2.5}$	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value

Abbreviation	Definition
LUM	lumacaftor
max	maximum value
MBW	multiple-breath washout
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum value
MMRM	mixed-effects model for repeated measures
n	number of subjects
OL-FAS	Open-label Full Analysis Set
OL-SS	Open-label Safety Set
PD	pharmacodynamics
PE	physical examination
PEx	pulmonary exacerbation
P-gp	P-glycoprotein
$ppFEV_1$	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
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
RD	respiratory domain
RNA	ribonucleic acid
RR	interval from the onset of 1 QRS complex to the next
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
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
ULN	upper limit of normal
US	United States
USA	United States of America

5 INTRODUCTION

5.1 Background

Cystic fibrosis (CF) is an autosomal recessive chronic disease with serious morbidities and frequent premature mortality. CF affects more than 70,000 individuals worldwide[1] (approximately 30,000 in the US[2] and 45,000 in the EU[3]). Based on its prevalence, CF qualifies as an orphan disease.[4, 5]

CF is caused by decreased quantity and/or function of the CFTR protein due to mutations in the *CFTR* gene.[6] CFTR is an ion channel that regulates the flow of chloride and other ions across epithelia in various tissues, including the lungs, pancreas and other gastrointestinal organs, and sweat glands.[7] Decreased CFTR quantity or function results in the failure to regulate chloride transport in these tissues leading to the multisystem pathology associated with CF.[8] In the lungs, obstruction of airways with thick mucus, establishment of a chronic bacterial infection in the airways, and damaging inflammatory responses are all thought to play a role in causing irreversible structural changes in the lungs, leading to respiratory failure. Progressive loss of lung function is the leading cause of mortality.[9]

The most common disease-causing *CFTR* mutation is *F508del*, which accounts for approximately 70% of the identified alleles in people with CF.[10] Approximately 40% to 45% of people with CF are homozygous for *F508del* (F/F), and approximately 85% have at least 1 *F508del* allele.[2, 3]

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 CFTR at the cell surface. Potentiators increase the channel open probability (channel gating activity) of the CFTR protein delivered to the cell surface to enhance ion transport. With differing mechanisms of action, a combination of correctors and potentiators increases F508del CFTR-mediated chloride transport more than either type of modulator alone.

The therapeutic activity of CFTR modulators has been established with products developed by Vertex Pharmaceuticals Incorporated and approved for the treatment of CF: ivacaftor (IVA) monotherapy (Kalydeco™), lumacaftor (LUM)/IVA (Orkambi™), and tezacaftor (TEZ)/IVA (Symdeko™, Symkevi™).

VX-445 is a next-generation CFTR corrector. In vitro, the triple combination (TC) of VX-445, TEZ, and IVA (VX-445/TEZ/IVA) increased CFTR chloride transport more than any of the dual combinations (VX-445/TEZ, VX-445/IVA, and TEZ/IVA) or individual components (VX-445, TEZ, and IVA) when added to human bronchial epithelial (HBE) cells derived from 2 groups of CF patients: those heterozygous for *F508del* with a second *CFTR* allele carrying a minimal function (MF) mutation that is not responsive to TEZ, IVA, and TEZ/IVA (F/MF genotypes); and those homozygous for *F508del* (F/F genotypes).

Additional information about VX-445/TEZ/IVA can be found in the Investigator's Brochure.

5.2 Study Rationale

This study will provide data on the long-term safety, efficacy, and durability of VX-445/TEZ/IVA in subjects with CF who are 6 years of age and older and who are homozygous or heterozygous for the *F508del* mutation.

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the long-term safety and tolerability of VX-445/TEZ/IVA in subjects with CF who are 6 years of age and older

6.2 Secondary Objective

To evaluate the long-term efficacy and pharmacodynamics (PD) of VX-445/TEZ/IVA

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, pulse oximetry, and ophthalmologic examinations

7.2 Secondary Endpoints

Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$)

Absolute change in sweat chloride (SwCl)

Absolute change in CFQ-R respiratory domain (RD) score

Absolute change in body mass index (BMI) and BMI-for-age z-score

Number of pulmonary exacerbations (PEx) and CF-related hospitalizations

Absolute change in lung clearance $index_{2.5}$ ($LCI_{2.5}$)

Absolute change in weight and weight-for-age z-score

Absolute change in height and height-for-age z-score

7.3 Other Endpoints

Absolute change in fecal elastase-1 (FE-1) levels

Absolute change in serum levels of immunoreactive trypsinogen (IRT)

8 STUDY POPULATION

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

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible. In the criteria below, "parent study" is defined as VX18-445-106 Part B, a Phase 3 study investigating VX-445/TEZ/IVA in subjects 6 years of age and older.

8.1 Part A

8.1.1 Inclusion Criteria

1. Subject (or his or her legally appointed and authorized representative) will sign and date an 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. Did not withdraw consent from the parent study.
4. Meets at least 1 of the following criteria:
   - Completed study drug treatment in the parent study, or
   - Had study drug interruption(s) in the parent study, but did not permanently discontinue study drug, and completed study visits up to the last scheduled visit of the Treatment Period of the parent study.
5. Willing to remain on a stable CF treatment regimen (as defined in Section 9.5) through completion of study participation.

8.1.2 Exclusion Criteria

1. History of any comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.
2. Pregnant or breast-feeding females. Female subjects must have a negative pregnancy test at the Part A Day 1 Visit before receiving the first dose of study drug.
3. History of drug intolerance in the parent study that would pose an additional risk to the subject in the opinion of the investigator (e.g., subjects with a history of allergy or hypersensitivity to the study drug).
4. Current participation in an investigational drug study other than the parent study, or the current study. Participation in a noninterventional study and screening for another Vertex study is permitted.

8.2 Part B

8.2.1 Inclusion Criteria

1. Subject (or his or her legally appointed and authorized representative) will sign and date an 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. Did not withdraw consent in Part A.
4. Meets at least 1 of the following criteria:
   - Completed study drug treatment in Part A, or
   - Had study drug interruption(s) in Part A, but did not permanently discontinue study drug, and completed study visits up to the last scheduled visit of the Treatment Period of Part A.

5. Willing to remain on a stable CF treatment regimen (as defined in Section 9.5) through completion of study participation.

8.2.2 Exclusion Criteria

5. History of any comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.
6. Pregnant or breast-feeding females. Female subjects must have a negative pregnancy test at the Part B Day 1 Visit before receiving the first dose of study drug.
7. History of drug intolerance in the parent study or in Part A of this study that would pose an additional risk to the subject in the opinion of the investigator (e.g., subjects with a history of allergy or hypersensitivity to the study drug).
8. Current participation in an investigational drug study other than the parent study, or the current study. Participation in a noninterventional study and screening for another Vertex study is permitted.

9 STUDY IMPLEMENTATION

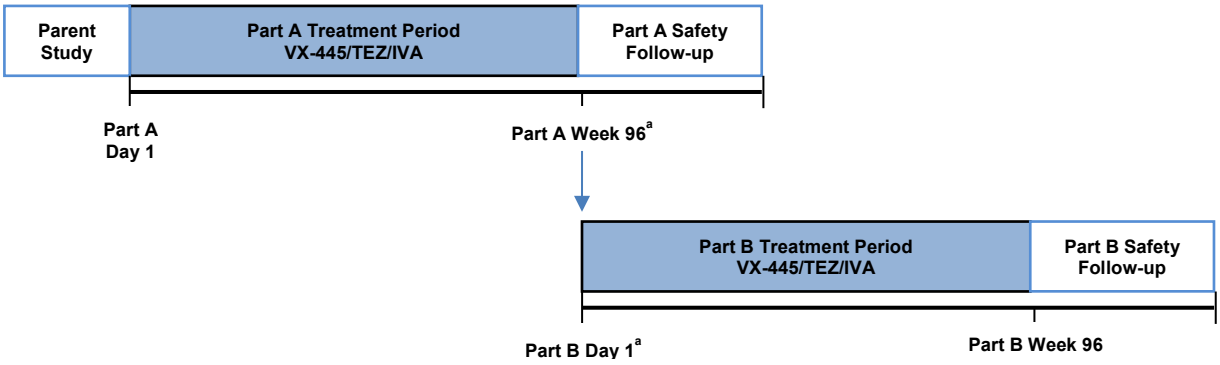
9.1 Study Design

This is a Phase 3, 2-part, multicenter, open-label extension study for subjects who completed the Treatment Period in the parent study (VX18-445-106 Part B) and meet eligibility criteria. The study design is shown in Figure 9-1.

Subjects who complete Part A will have the opportunity to enroll in Part B for an additional 96 weeks.

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.

Figure 9-1 Schematic of the Study Design



IVA: ivacaftor; TEZ: tezacaftor
Note: The parent study is VX18-445-106 Part B, a Phase 3 study investigating VX-445/TEZ/IVA in subjects 6 through 11 years of age. The figure is not drawn to scale.
[a] Subjects whose Part B Day 1 Visit is on the same day or within 1 calendar day of the Part A Week 96 Visit do NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 96 Visit. Subjects whose Part B Day 1 Visit is more than 1 calendar day after the Part A Week 96 Visit must complete all assessments specified for the Part A Week 96 AND Part B Day 1 Visits.

All subjects will receive VX-445/TEZ/IVA at the weight-appropriate dosage levels for 96 weeks in Part A. In Part B, subjects will receive VX-445/TEZ/IVA at age- and weight-appropriate dosage levels for 96 weeks (Table 9-1).

Table 9-1 Treatment Period Dosages

Subject Weight	VX-445 Dosage	TEZ Dosage	IVA Dosage
Part A, subjects ≥6 years of age			
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
<30 kg	100 mg qd	50 mg qd	75 mg q12h
Part B, subjects ≥6 to <12 years of age			
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
<30 kg	100 mg qd	50 mg qd	75 mg q12h
Part B, subjects ≥12 years of age			
All weights	200 mg qd	100 mg qd	150 mg q12h

IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor
Note: Study drug administration is described in Section 9.6.

Part A:

Subjects weighing ≥30 kg at the Part A Day 1 Visit will receive 200 mg VX-445 once daily (qd)/100 mg TEZ qd/150 mg IVA every 12 hours (q12h) for the duration of the study. Subjects weighing <30 kg at the Part A Day 1 Visit will receive 100 mg VX-445 qd/50 mg TEZ qd/75 mg IVA q12h. If a subject enters the current study weighing <30 kg and subsequently weighs ≥30 kg at 2 consecutive clinic visits, the dose will be adjusted to the higher dose of 200 mg VX-445 qd/100 mg TEZ qd/150 mg IVA q12h for the remainder of the study, starting with the second visit where subject's weight is ≥30 kg.

Part B:

In Part B, subjects will receive 200 mg VX-445 qd/100 mg TEZ qd/150 mg IVA q12h if they meet any of the following criteria:

- Subject is ≥12 years of age
- Subject received 200 mg VX-445 qd/100 mg TEZ qd/150 mg IVA q12h in Part A
- Subject is ≥30 kg on Part B Day 1

All other subjects <12 years of age and <30 kg will receive 100 mg VX-445 qd/50 mg TEZ qd/75 mg IVA q12h until either:

- The subject weighs ≥30 kg at 2 consecutive clinic visits in Part B, or
- The subject turns 12 years of age

Once either of the above criteria are met, the subject will receive 200 mg VX-445 qd/100 mg TEZ qd/150 mg IVA q12h for the remainder of the study.

9.1.1 Treatment Period

Treatment Period assessments are listed in Table 3-1 and Table 3-2.

Part A:

Subjects will receive the first dose of study drug on Part A Day 1 after obtaining informed consent (and assent, when applicable) and confirming eligibility. Subjects who enroll in this study on a study drug interruption will NOT receive the first dose of study drug until they meet the resumption criteria in Section 9.8; before receiving study drug, subjects will repeat all Part A Day 1 assessments.

Study drug administration details are provided in Section 9.6.

Subjects whose Part A Day 1 Visit is NOT within 1 day of the last scheduled visit of the parent study will repeat all Part A Day 1 assessments.

Subjects whose Part A Day 1 Visit is within 1 day of the last scheduled visit of the parent study will NOT have to repeat any Part A Day 1 assessments that were specified to be performed at the last scheduled visit in the parent study.

Part B:

For subjects who elect to enroll in Part B, the Part A Week 96 Visit will be the start of treatment in Part B (i.e., Part B Day 1).

Subjects whose Part B Day 1 Visit is on the same day or within 1 calendar day of the Part A Week 96 Visit do NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 96 Visit. Subjects whose Part B Day 1 Visit is more than 1 calendar day after the Part A Week 96 Visit must complete all assessments specified for the Part A Week 96 AND Part B Day 1 Visits.

9.1.2 Safety Follow-up

In Parts A and B, the Safety Follow-up Visit is scheduled to occur 28 (± 7) days after the last dose of study drug. The Safety Follow-up Visit assessments are listed in Table 3-1 and Table 3-2.

The Safety Follow-up Visit is required for all subjects. However, subjects will complete the respective Part A or Part B Week 96 Visit and will not have a Safety Follow-up Visit if the subject transitions within 28 days of the last dose of study drug to one of the following:

- A commercially available Vertex CFTR modulator regimen,
- Managed-access-program-supplied Vertex CFTR modulator regimen,
- Or, to another Part of the current study or another qualified Vertex study.

If the transition occurs before the Week 96 Visit, then subjects will complete the Early Termination of Treatment (ETT) Visit. In these cases, the Week 96 Visit or the ETT Visit, whichever is applicable, will replace the Safety Follow-up Visit.

For subjects who complete an ETT Visit 3 weeks or later following the last dose of study drug, the ETT Visit will replace the Safety Follow-up Visit (Section 9.1.3).

9.1.3 Early Termination of Treatment

If a subject prematurely discontinues study drug treatment, an ETT Visit should be scheduled as soon as possible after the decision to discontinue treatment.

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

If a subject 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.

9.1.4 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.

9.1.5 Completion of Study Participation

Completion of study participation for each individual subject is defined as: the Safety Follow-up Visit; or, in situations in which the ETT Visit or the Part A or B Week 96 Visit replaces the Safety Follow-up Visit (Section 9.1.2), the ETT Visit or Part A or B Week 96 Visit.

If subjects withdraw consent or assent, completion of study participation is defined as date of withdrawal of consent or assent, whichever is earlier (Section 9.9).

If subjects are lost to follow-up (Section 9.1.4), the date of completion of study participation will be defined as the date of last contact.

The end of study is defined in Section 13.2.8.

9.1.6 Independent Data Monitoring Committee

This study will be monitored by an independent data monitoring committee (IDMC), which will conduct periodic reviews of safety data from the study (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 enrolled.

9.2 Method of Assigning Subjects to Treatment Groups

This is an open-label study. Randomization is not required because all subjects will be treated identically in a single cohort. An interactive web response system (IWRS) will be used to dispense dosage based on subject weight and age.

9.3 Rationale for Study Elements

9.3.1 Study Design

This Phase 3 study will enroll subjects who completed the last treatment period visit in the parent study of VX-445/TEZ/IVA and meet eligibility criteria. Results from this study will provide information on the long-term safety and efficacy of TC treatment with VX-445/TEZ/IVA in subjects with CF who are 6 years of age and older and homozygous or heterozygous for the *F508del* mutation.

9.3.2 Study Drug Dose and Duration

To evaluate long-term safety, tolerability, and efficacy, the study drug doses evaluated are the same as the doses evaluated in the parent study. Subjects will receive a study drug dose appropriate for their weight, as described in Section 9.1.

The overall treatment duration of 96 weeks in each Part was used in open-label extension studies for previously approved CFTR modulators, and is considered sufficient for the evaluation of long-term safety and efficacy.

9.3.3 Rationale for Study Assessments

The safety, efficacy, and PD assessments are standard parameters for clinical studies in drug development and are generally recognized as reliable, accurate, and relevant to the study of subjects with CF. Baseline and follow-up ophthalmologic examinations are recommended for monitoring of pediatric patients treated with regimens containing IVA, and have been included in the standard safety assessments.

Obstruction of airways with thick mucus, chronic bacterial infection of the airways, and the inflammatory response all play a role in causing lung damage in CF. Therefore, assessment of inflammatory mediators such as IRT and other biomarkers is included.

LCI is a measure of ventilation inhomogeneity that is based on tidal breathing techniques that have been evaluated in patients as young as infants.[11, 12] Studies have shown that LCI correlates with FEV_1 in its ability to measure airway disease and can detect lung disease at an earlier stage

than spirometry.[13, 14] Furthermore, data from Studies VX10-770-106 and VX14-809-109 in CF patients with an FEV_1 >90% showed LCI to be a more sensitive outcome measure than FEV_1.

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. Guidance for concomitant medications is provided in Section 9.5.

Table 9-2 Prohibited Medications

	Timing of Restriction		
Medication	**Start of Restriction**	**End of Restriction**	**Rationale**
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug on Part A Day 1	None allowed through completion of study participation	VX-445, TEZ, and IVA are metabolized extensively via CYP3A4. Therefore, use of moderate and strong inducers of CYP3A and moderate and strong inhibitors of CYP3A, which have the potential to alter the exposure of VX-445, TEZ, or IVA, will be prohibited.
Moderate and strong CYP3A inhibitors (except ciprofloxacin)[a]	None allowed within 14 days before the first dose of the study drug on Part A Day 1	None allowed through completion of study participation	
CFTR modulators (investigational or approved), except for study drugs in the parent study and this study	None allowed within 28 days or 5 terminal half-lives (whichever is longer) before the first dose of the study drug on Part A Day 1	None allowed until after the last dose of study drug	These agents may confound the results of this study.

IVA: ivacaftor; TEZ: tezacaftor

[a] 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).

9.5 Prior and Concomitant Medications

Information regarding prior and concomitant medications, including CF medications, other medications, and herbal and naturopathic remedies, will be collected in each subject's source documentation for medications taken within the 56 days before the first dose of study drug in this study through completion of study participation, as defined in Section 9.1.5.

- Subjects should remain on a stable treatment regimen for their CF 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 Part A Day 1. Subjects should not initiate long-term treatment with new medication from 28 days before the Part A Day 1 Visit through completion of study participation. Guidelines for stable treatment regimens for CF are as follows:

  - Subjects who are taking inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
  - Subjects who cycle onto and off of an inhaled antibiotic should continue on their prior schedule.
  - Subjects who alternate between 2 different inhaled antibiotics should remain on the same cycling schedule during the study.
- 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.
- VX-445 may inhibit OATP1B1 and OATP1B3, which may increase the exposure of medicinal products that are substrates for these transporters. Substrates such as statins, glyburide, nateglinide, and repaglinide should be used with caution.
- IVA is a weak inhibitor of P-glycoprotein (P-gp). Administration of IVA may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. Digoxin or other substrates of P-gp with a narrow therapeutic index, such as cyclosporine, everolimus, sirolimus, and tacrolimus, should be used with caution and appropriate monitoring.
- IVA may inhibit CYP2C9; therefore, during coadministration with warfarin, additional monitoring of the international normalized ratio is recommended. Other medicinal products that are CYP2C9 substrates for which exposure may be increased include glimepiride and glipizide; these should be used with caution.
- Information about bronchodilator use during the study will be collected and documented. Subjects who are using a bronchodilator should have their spirometry assessments performed according to the guidelines provided in Section 11.3.1.

9.6 Administration

9.6.1 Dosing

Study drug will be administered orally. Additional information is provided in the Pharmacy Manual.

Study drug should 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 VX-445/TEZ/IVA tablets in the morning and as 1 IVA tablet in the evening. For each subject, doses of study drug should be taken at approximately the same time (± 2 hours) each day.
3. On days of scheduled visits, the morning dose of VX-445/TEZ/IVA 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 VX-445/TEZ/IVA.

4. If a subject's scheduled clinic visit is to occur in the afternoon, the following guidelines should 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 VX-445/TEZ/IVA and the morning dose of VX-445/TEZ/IVA 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 of VX-445/TEZ/IVA, the subject should take the morning dose of VX-445/TEZ/IVA at home.
5. 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

If 6 hours or less have passed since the missed morning or evening dose, the subject should take the missed dose as soon as possible and continue on the original schedule.

Morning dose: If more than 6 hours have passed since the missed **morning** dose, the subject should take the missed dose as soon as possible and should not take the evening dose.

Evening dose: If more than 6 hours have passed since the missed **evening** dose, the subject should not take the missed dose. The next scheduled morning dose should be taken at the usual time.

Morning and evening doses should not be taken at the same time.

9.7 Dose Modification for Toxicity

Modifications of the study drug dose are prohibited. Should any unacceptable toxicity arise, individual subjects will be withdrawn from the study and dosing will cease.

9.8 Study Drug Interruption and Stopping Rules

In subjects who have interrupted study drug for >72 hours for any reason, the investigator should resume study drug only after a thorough investigation of the cause for interruption. The investigator will evaluate the subject's clinical stability and should consider resumption of study drug only after the subject is clinically stable and there is no comorbidity or condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.

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. In subjects for whom study drug was previously interrupted, the medical monitor should be notified of any plan to discontinue study drug, before the discontinuation has occurred, if possible.

9.8.1 Liver Function Tests

The central laboratory will notify the medical monitor of alanine transaminase (ALT) or aspartate transaminase (AST) >3 × upper limit of normal (ULN) and total bilirubin >2 × ULN that are derived from centrally submitted samples.

Subjects with new treatment-emergent ALT or AST elevations of >3 × ULN, with or without total bilirubin >2 × 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 × ULN
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN, in association with total bilirubin >2 × ULN and/or clinical jaundice

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

Study drug administration **must be discontinued** if the following criteria are 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 transaminase levels return to baseline or are ≤2 × ULN, whichever is higher. Regardless of the duration of interruption, the medical monitor should be notified before 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 (Section 13.1.1.4), or a rash that is considered a serious adverse event (SAE). The investigator will notify the medical monitor of any rash that results in interruption of study drug, is Grade 3 or higher, or is an SAE. Investigators should consider additional evaluation including laboratory testing (e.g., complete blood count with differential, liver function tests), 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.

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

- Meets any of the stopping (discontinuation) criteria (Section 9.8)
- Becomes pregnant (Section 11.5.6.2)

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 9.1.2), 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 compounds, 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 or her information from the study data. A subject may request destruction of the samples collected from him or her during the study as long as those samples can be identified as his or her samples.

9.10 Replacement of Subjects

Subjects who withdraw or are withdrawn during the study drug Treatment Period will not be replaced.

10 STUDY DRUG INFORMATION AND MANAGEMENT

Study drug refers to VX-445/TEZ/IVA and IVA.

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

Study drug will be supplied as film-coated tablets (Table 10-1). 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. Detailed instructions regarding the storage, handling, and dispensation of the study drug will be provided in the Pharmacy Manual.

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

Drug Name, Dosing Form, Route	Tablet Strength (Subjects ≥12 Years or ≥30 kg)	Tablet Strength (Subjects <12 Years and <30 kg)
VX-445/TEZ/IVA, FDC tablet, oral		
VX-445	100 mg	50 mg
TEZ	50 mg	25 mg
IVA	75 mg	37.5 mg
IVA, tablet, oral	150 mg	75 mg

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

10.4 Drug Accountability

The pharmacist or designated study site staff will maintain information about 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 or 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 an open-label study; however, subjects and their legally appointed and authorized representative (e.g., parent or legal guardian) should not be informed of their study-related spirometry and LCI, SwCl, FE-1, and IRT results until the study has been completed, regardless if the subject permanently discontinues treatment. In addition, the Vertex study team will not

have access to the spirometry, LCI, or SwCl results of the present study until the database lock of the parent study.

11 ASSESSMENTS

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

11.1 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, and weight. Select demographic and medical history will be derived from the parent study.

11.2 Pharmacokinetics

Not applicable.

11.3 Efficacy and Pharmacodynamics

11.3.1 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines[15] 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®]) 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®]) for more than 24 hours before the spirometry assessment.

At all visits, all spirometry assessments should be performed pre-bronchodilator. During the Treatment Periods, 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 Part A 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 Part A Day 1, the subject forgets to withhold his or her dose of bronchodilator, spirometry should be performed post-bronchodilator, and all subsequent spirometric measurements (according to the schedule of assessments) 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.

See Section 10.7 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 Global Lung Function Initiative (GLI).[16]

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

11.3.2 Sweat Chloride

The SwCl test is a standard diagnostic tool for CF, serving as a biomarker of CFTR activity. Sweat samples will be sent to a central laboratory for testing and interpretation of results. Individual SwCl test results will not be disclosed to the study sites. Specific instructions for collection, handling, processing, and shipping of SwCl samples to the central laboratory will be provided separately. The SwCl test must be conducted predose relative to the morning dose of study drug during the Treatment Periods. At each time point, 2 samples will be collected, 1 sample from each arm (left and right).

See Section 10.7 for information about access to SwCl results.

11.3.3 Multiple Breath Washout

The N_2-MBW testing will be performed in multiple replicates for each visit and the final LCI value will be calculated from the technically acceptable washout replicates by a central reader. The final LCI value at each visit will be the value provided by the LCI vendor based on the replicates.

At all visits, MBW tests should be performed "pre-bronchodilator" as described in Section 11.3.1. The MBW test should be performed before the spirometry assessment. See Section 10.7 for information about access to LCI results.

Detailed MBW procedures will be supplied separately in a Study Reference Manual.

11.3.4 Height and Weight

Height and weight will be measured with shoes off and before the dose of the study drug at each clinic visit during the Treatment Periods.

11.3.5 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/caregivers will be asked to complete the CFQ-R in their native language, if validated translations are available.[17, 18] 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 with non-English-speaking populations.[19, 20]

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

11.3.6 Other Events Related to Outcome

11.3.6.1 Antibiotic Therapy for Sinopulmonary Sign/Symptoms

New or changed antibiotic therapy (intravenous [IV], inhaled, or oral) for the following sinopulmonary signs/symptoms will be determined and documented at visits as indicated in Table 3-1 and 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.[21, 22]

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.

11.3.6.2 Hospitalization for CF

Subjects will be queried about planned and unplanned hospitalizations lasting ≥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.

11.4 Other Assessments

These data will be used for internal exploratory purposes and may or may not be included in the clinical study report (CSR). Detailed procedures for the collection of blood samples will be provided in a separate document.

11.4.1 FE-1 and IRT

Assessments of FE-1 and IRT will be conducted to assess exocrine pancreatic function.

Fecal samples for assessment of FE-1 will be collected at the study center during the study visit; alternatively samples may be collected by the subject's caregiver up to 24 hours before the study visit (e.g., at home) and brought to the study visit. The sample may be collected pre- or postdose.

See Section 10.7 for information about access to FE-1 and IRT results.

11.4.2 Blood Biomarkers

Blood samples for blood biomarker analysis will be collected and banked for potential exploratory evaluation of correlations between blood biomarkers (e.g., proteins, peptides, lipids, vitamins, endogenous metabolites, and RNA) with PD, treatment benefit, and AEs.

Specific instructions for the collection, processing, storage, and shipment of blood biomarker samples will be provided in the Laboratory Manual.

11.5 Safety

Safety evaluations will include reporting of AEs, clinical laboratory assessments, PEs, clinical evaluation of vital signs, pulse oximetry, standard 12-lead ECGs, and ophthalmologic examinations.

11.5.1 Adverse Events

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

11.5.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory with the exception of urine pregnancy tests, which will be analyzed locally. All blood samples will be collected while subjects are in a seated or supine position. Specific instructions for the collection, processing, and shipment of samples will be provided in a separate Laboratory Manual. Laboratory test results that are abnormal and considered clinically significant must be reported as AEs (see Section 13.1).

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

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis[a]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen[b]	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	**Coagulation**	
Alanine transaminase	Activated partial thromboplastin time	
Amylase	Prothrombin time	
Lipase	Prothrombin time International Normalized Ratio	
Gamma-glutamyl transferase		
Protein		
Albumin		
Creatine kinase		
Total cholesterol		
Lactate dehydrogenase		

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

[a] 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.

[b] If blood urea nitrogen cannot be collected, urea may be substituted.

Pregnancy (β-human chorionic gonadotropin) Tests for all Female Subjects: All female subjects must have a pregnancy test every 4 weeks. Serum pregnancy tests will be performed at the study site and analyzed at the central laboratory. Urine pregnancy tests will be performed and analyzed at the site or, at assessment time points when telephone contact takes the place of a clinic visit, at home by using a home kit provided by the study site. Results of a home urine pregnancy test will be reported to the site by telephone. Additional pregnancy tests may be required according to local regulations and/or requirements.

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

For the purposes of study conduct and unless noted otherwise, 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.

11.5.3 Physical Examinations and Vital Signs

A PE of all body systems and vital signs assessment will be performed at select study visits. At other visits, symptom-directed PEs and symptom-directed vital signs assessments can be performed at the discretion of the investigator or healthcare provider.

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

Weight, height, and BMI (derived) will also be assessed (Section 11.3.4).

Vital signs include blood pressure (systolic and diastolic), temperature, pulse rate, and respiration rate. These will be assessed following at least a 5-minute rest in the seated or supine position.

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.

11.5.4 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout. Additional standard 12-lead ECGs will be performed at any other time if clinically indicated. The performance of all ECGs will adhere to the following guidelines:

- The ECG will be done before any other procedures that may affect heart rate, such as blood draws.
- The subject will be instructed to rest for at least 5 minutes before having an ECG.

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 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 ≥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 ≥500 msec), a single ECG will be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. A subject with a QTcF value above the threshold value will discontinue dosing.

11.5.5 Ophthalmologic Examination

Ophthalmologic examinations do 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.

Ophthalmologic examinations are required at select study visits in the Treatment Periods (Table 3-1 and Table 3-2). These examinations should be completed within 4 weeks of the relevant study visit. An ophthalmologic examination is also required at the ETT Visit for subjects whose cumulative VX-445/TEZ/IVA exposure (in the parent study and current study) is at least 12 weeks since the last study ophthalmologic examination.

Any clinically significant abnormal findings will be reported as AEs.

11.5.6 Contraception and Pregnancy

The effects of VX-445 monotherapy or in TC with TEZ and IVA on conception, pregnancy, and lactation in humans are not known. VX-445, 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-445, TEZ, and IVA have not shown teratogenicity in rats and rabbits.

11.5.6.1 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 date of informed consent 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:
    - Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females
    - 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 11-2.

Table 11-2 Acceptable Methods of Contraception

	Male Subjects and Their Female (Non-study) Partners	Female Subjects and Their Male (Non-study) Partners
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[a]	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		
Hormone-releasing	Yes	Yes
Non-hormone releasing	Yes	Yes
Oral, implanted, injected, or vaginal **hormonal** contraceptives, if successfully used for at least 60 days before the first dose of study drug	Yes	Yes

[a] A female condom cannot be used with a male condom due to risk of tearing.

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 11-2.
- If over the course of the study the subject's status changes and the subject does not meet the criteria for waiving the contraception requirements, the subject must begin following the contraceptive methods listed in Table 11-2.
- 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.

11.5.6.2 Pregnancy

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

If a subject, or the female partner of a male subject, becomes pregnant during study participation, study drug will be permanently discontinued immediately. The investigator will 1) notify the medical monitor and Vertex Global Patient Safety (GPS) within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy, and 2) send the Pregnancy Information Collection Form to Vertex GPS. 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.

Provided informed consent is obtained, 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. 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), which will be finalized before the clinical data lock for the study.

12.1 Sample Size

The primary and secondary objectives of the study are the evaluation of the long-term safety, tolerability, and efficacy of VX-445/TEZ/IVA. This is an open-label study that will enroll subjects who complete study treatment in the parent study and meet eligibility criteria. Approximately 56 subjects are expected to enroll in this open-label study.

12.2 Analysis Sets

The following analysis sets will be defined for Part A and Part B separately:

The **Open-label All Subjects Set** for Part A or B is defined as all subjects who were enrolled (defined as subject having data in the corresponding clinical database) in the corresponding Part. This analysis set will be used for individual subject data listings and disposition summary tables unless otherwise specified.

The **Open-label Full Analysis Set (OL-FAS)** for Part A or B is defined as all enrolled subjects who have received at least 1 dose of study drug in the corresponding Part. The OL-FAS will be used to summarize subject demographics and baseline characteristics and for all efficacy analyses unless otherwise specified.

The **Open-label Safety Set (OL-SS)** for Part A or B is defined as all subjects who have received at least 1 dose of study drug in the corresponding Part. The OL-SS will be used for all safety analyses unless otherwise specified.

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 the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the parent study. For assessments collected in replicates, the baseline will be defined as the average of non-missing values.

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

The **Efficacy Analysis Period** for each Part will include the time from the first dose of study drug to the last scheduled efficacy visit in the corresponding Part, unless otherwise specified.

The **Treatment-emergent (TE) Period** for each Part will include the time from the first dose of study drug to 28 days after the last dose of the study drug or to the date of completion of study participation in the corresponding Part (as defined in Section 9.1.5), whichever occurs first.

Part A and Part B data will be analyzed separately, using the respective analysis set, efficacy analysis period, and TE period for each Part. For analysis of the number of PEx, events in the parent study and this study (Parts A and B, as applicable) may also be combined.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

Subject disposition will be summarized separately for each Part for the Open-label All Subjects Set. The number and percentage of subjects in the following categories will be summarized as appropriate:

- Open-label All Subjects Set
- Dosed (OL-SS)
- Enrolled and dosed (OL-FAS)
- Completed treatment
- Prematurely discontinued treatment and the reasons for discontinuation
- Completed study
- Prematurely discontinued the study and the reasons for discontinuation

12.3.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized separately for each Part by descriptive summary statistics. Baseline characteristics will be the same as the parent study baseline characteristics.

The following demographics and baseline characteristics will be summarized for the OL-FAS and will include (but are not limited to) sex, race, ethnicity, baseline age, baseline weight, baseline height, baseline BMI, baseline ppFEV$_1$, baseline SwCl, and baseline CFQ-R RD score.

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

12.3.2.3 Prior and Concomitant Medications

Medications will be coded using WHODrug and categorized as follows:

- **Prior medication:** any medication that was administered within the 56 days before the first dose of study drug in each Part
- **Concomitant medication:** medication continued or newly received during the TE Period in each Part
- **Post-treatment medication:** medication continued or newly received after the TE Period in each Part

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 initial dosing, concomitantly during the TE Period, or beyond 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 OL-FAS, separately for each Part. 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 separately for each Part based on the OL-SS, defined as the last day of study drug in each Part minus the first day of study drug in each Part plus 1, regardless of study drug interruption.

Study drug compliance will be summarized based on the OL-FAS, and will be calculated as: $100 \times [1 – (\text{total number of days of study drug interruption in each Part}) / (\text{duration of study drug exposure in days in each Part})]$. 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 based on the OL-FAS, and will be calculated as: $100 \times [(\text{total number of tablets dispensed in each part}) – (\text{total number of tablets returned in each Part})] / (\text{total number of tablets planned to be taken per day} \times \text{duration of study drug exposure in days for each Part})$.

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 wellbeing. 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 Analyses

The secondary objective of the study is the evaluation of the long-term efficacy and PD of VX-445/TEZ/IVA.

12.3.3.1 Analysis of Primary Endpoint

Not applicable. Efficacy and PD are not primary objectives.

12.3.3.2 Analysis of Secondary Efficacy and Pharmacodynamic Endpoints

The secondary endpoints will be analyzed separately for each Part.

- **Absolute change in ppFEV$_1$**

One of the secondary efficacy endpoints is the absolute change from baseline in ppFEV$_1$ at visits in this open-label study, for subjects who receive at least 1 dose of study drug in each Part. The primary analysis for this secondary endpoint will be based on a mixed-effects model for repeated measures (MMRM), with the absolute change from baseline in ppFEV$_1$ as the dependent variable for visits in each Part. The model will be similar to the one used in the parent study.

The details including sensitivity analyses and supportive analysis will be described in the SAP.

- **Absolute change in SwCl**

Analysis of this PD endpoint will be based on an MMRM similar to the one used in the parent study.

- **Absolute change in CFQ-R RD score**

Analysis of this endpoint will be based on an MMRM similar to the one used in the parent study.

- **Absolute change in BMI and BMI-for-age z-score**

Analysis of this endpoint will be based on an MMRM similar to the one used in the parent study.

- **Number of PEx and CF-related hospitalizations**

Analysis of this endpoint will be based on summary statistics. Additional analysis may be provided and details will be discussed in the SAP.

- **Absolute change in LCI$_{2.5}$**

Analysis of this endpoint will be based on an MMRM similar to the one used in the parent study.

- **Absolute change in weight and weight-for-age z-score**

Analysis of this endpoint will be based on an MMRM similar to the one used in the parent study.

- **Absolute change in height and height-for-age z-score**

Analysis of this endpoint will be based on an MMRM similar to the one used in the parent study.

12.3.3.3 Multiplicity Adjustment

Not applicable.

12.3.4 Safety Analysis

The primary objective of the study is the evaluation of the long-term safety and tolerability of VX-445/TEZ/IVA. Data from Part A and Part B will be analyzed separately. For each Part, all safety analyses will be based on the TE Period for subjects in the OL-SS, unless otherwise specified.

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

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

All safety data will be presented in individual subject data listings. Only descriptive analyses of safety data will be performed.

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 of study drug in the TE Period in each Part
- **TEAE:** any AE that worsened (either in severity or seriousness) or newly developed at or after the first dose date of study drug in the TE Period in each Part
- **Post-treatment AE:** any AE that worsened (either in severity or seriousness) or newly developed after the TE Period in each Part

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 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. An AE

overview table will be provided. 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.

Exposure-adjusted event rates may also be provided.

12.3.4.2 Clinical Laboratory Assessments

For the treatment-emergent laboratory measurements, the observed values and change from baseline values of the continuous laboratory parameters will be summarized in SI units at each time point during the TE Period in each Part.

The number and percentage of subjects with at least 1 threshold analysis event during the TE Period in each Part will be summarized. The shift of the threshold analysis criteria from baseline to post-baseline will also be summarized for selected laboratory parameters. The threshold analysis and 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 laboratory assessment values will be provided. This listing will include data from scheduled and unscheduled time points.

Additional safety laboratory data analyses may be described in the SAP.

12.3.4.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided at each time point during the TE Period in each Part, for the following standard 12-lead ECG interval measurements (in msec): RR, PR, QT, QTc for heart rate (HR) interval (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 in this open-label study will be summarized. 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 at each time point during the TE Period in each Part. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute).

The number and percentage of subjects with at least 1 threshold analysis event during the TE Period in each Part will be summarized. 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 at each time point during the TE Period in each Part, 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.

12.3.4.6 Physical Examination

No tables/figures/listings will be provided for PE data.

12.3.4.7 Other Safety Analyses

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

12.3.5 Other Analyses

Details of other analyses, including FE-1 and IRT, will be provided in a separate document.

12.3.6 Interim and IDMC Analyses

12.3.6.1 Interim Analysis

Interim analyses may take place at any time at the discretion of the sponsor.

12.3.6.2 IDMC Analysis

The IDMC (Section 9.1.6) will conduct regular safety reviews of study data as outlined in the IDMC charter.

The IDMC's objectives, responsibilities, and operational details will be defined in a separate document (IDMC charter), which will be finalized before the first subject is enrolled in the study.

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 completion of study participation (Section 9.1.5).

All subjects' parents or legal guardians 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. 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 5.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed February 2019). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." When 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 in the CTCAE. The severity of an AE described by a term that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

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

AE: adverse event

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 in Table 13-2.

Table 13-2 Classifications for AE Causality

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

AE: adverse event

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 in Table 13-3.

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

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

AE: adverse event

[a] Refer to Sections 9.7 and 9.8 for directions regarding what drug actions are permitted per protocol.

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 in Table 13-4.

Table 13-4 Classifications for Outcome of an AE

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

AE: adverse event

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 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 Reporting and Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through the Safety Follow-up Visit, regardless of causality, will be reported by the investigator to Vertex GPS **within 24 hours of identification**. In addition, all SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours of identification**.

For SAEs that occur after obtaining informed consent and assent (where applicable) through the Safety Follow-up Visit, 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: globalpatientsafety@vrtx.com (preferred choice)

Fax: +1-617-341-6159

For technical issues related to submitting the form, contact telephone: +1-617-341-6677

SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be recorded on the Vertex Clinical Trial 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 the outcome to Vertex using the SAE Form.

13.1.2.3 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/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 be conducted only at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

13.2.2 Subject Information and Informed Consent

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

13.2.3 Investigator Compliance

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

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all data provided to Vertex, study reports, and communications relating to

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

For sites participating in the US, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated regulations, an executed HIPAA authorization will be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization will 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 scheduled contact) of the last subject.

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. Vertex will provide, or assess and approve, any electronic data capture (EDC) tools.

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 subject. Data collected during the study will be recorded in a data capture system for each enrolled subject. Each subject's set of captured data records, once complete, will be signed and dated by the investigator.

13.4 Monitoring

The study will be monitored by Vertex or its designee in accordance with written procedures. Monitoring and auditing procedures developed or approved by Vertex for these activities comply with GCP regulatory requirements and guidelines. The monitoring strategy may include onsite, remote, and central monitoring activities, in accordance with local regulations. The study site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

13.5 Electronic Data Capture

Sites will use an EDC tool to record data for each enrolled subject.

It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported. 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 subject, including the dates and details of study procedures, AEs, other observations, and subject status.

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 data reported to Vertex, including any changes made, to endorse the final submitted data for the subjects for whom the investigator is responsible.

13.6 Confidentiality and Disclosure

Any and all scientific, commercial, and technical information disclosed by Vertex in this protocol or elsewhere will be considered the confidential and proprietary property of Vertex. The investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The investigator shall not use such information for any purpose other than determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The investigator understands that the information developed from this clinical study will be used by Vertex in connection with the development of the study drug and other drugs and diagnostics, and therefore may be disclosed as required to other clinical investigators, business partners and associates, the FDA, and other government agencies. The investigator also understands that, to

allow for the use of the information derived from the clinical study, the investigator has the obligation to provide Vertex with complete test results and all data developed in the study.

13.7 Publications and Clinical Study Report

13.7.1 Publication of Study Results

Vertex is committed to reporting the design and results of all clinical studies in a complete, accurate, balanced, transparent, and timely manner, consistent with Good Publication Practices (GPP3).[23]

Publication Planning: Vertex staff along with the lead principal investigators, the steering committee, and/or the publication committee will work together to develop a publication plan.

Authorship: Authorship of publications will be determined based on the Recommendations for Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states that authorship should be based on the following 4 criteria[24]:

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2. Drafting of the article or revising it critically for important intellectual content;
3. Final approval of the version to be published; and
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet conditions 1, 2, 3, and 4. All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Contributions such as medical writing, enrollment of subjects, acquisition of funding, collection of data, or general supervision of the research group, alone, do not justify authorship.

Contributors: Contributors who meet fewer than all 4 of International Committee of Medical Journal Editors criteria for authorship will not be listed as authors, but their contribution will be acknowledged and specified either as a group (e.g., “study investigators”) or individually (e.g., “served as scientific advisor”).

Publication Review: As required by a separate clinical study agreement, Vertex must have the opportunity to review all publications, including any manuscripts, abstracts, oral/slide presentations, and book chapters regarding this study before submission to congresses or journals for consideration.

13.7.2 Clinical Study Report

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

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX19-445-107	Version #: 2.0	Version Date: 10 June 2021
Study Title: A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445/TEZ/IVA Combination Therapy in Subjects With Cystic Fibrosis Who Are 6 Years of Age and Older		

[redacted]

15.2 Investigator Signature Page

Protocol #: VX19-445-107	Version #: 2.0	Version Date: 10 June 2021
Study Title: A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445/TEZ/IVA Combination Therapy in Subjects With Cystic Fibrosis Who Are 6 Years of Age and Older		

I have read Protocol VX19-445-107, Version 2.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-445, TEZ, IVA and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

_____
Printed Name

_____ _____
Signature Date