1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the *F508del* Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes)

Vertex Study Number: VX18-445-104

[redacted]

EudraCT Number: 2018-002835-76

Date of Protocol: 02 December 2019 (Version 2.0)

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Summary of Changes to the Protocol

The previous version of this protocol (Version 1.0, 30 May 2019) was amended to create the current version (Version 2.0, 02 December 2019). The protocol history is provided below.

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.0, 30 May 2019	Original version
Version 2.0, 02 December 2019	Current version

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

Change and Rationale	**Affected Sections**
Absolute change in BMI from baseline at Week 8 was added as an exploratory endpoint to meet an FDA post-marketing commitment.	Sections 2, 7.3, and 12.3.3.5

2 PROTOCOL SYNOPSIS

Title A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the *F508del* Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes)

Brief Title A Phase 3 Study of VX-445 Combination Therapy in Cystic Fibrosis (CF) Subjects Heterozygous for *F508del* and a Gating or Residual Function Mutation (F/G and F/RF Genotypes)

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

Objectives

Primary Objective

To evaluate the efficacy of VX-445/tezacaftor (TEZ)/ivacaftor (IVA) in CF subjects who are heterozygous for *F508del* and a gating or residual function mutation (F/G and F/RF genotypes)

Secondary Objectives

- To evaluate the safety of VX-445/TEZ/IVA
- To evaluate the pharmacodynamics (PD) of VX-445/TEZ/IVA

Endpoints

Primary Endpoint

Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline through Week 8 for the VX-445/TEZ/IVA group

Key Secondary Endpoints

- Absolute change in sweat chloride (SwCl) from baseline through Week 8 for the VX-445/TEZ/IVA group
- Absolute change in $ppFEV_1$ from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group
- Absolute change in SwCl from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group

Other Secondary Endpoints

- Absolute change in CF Questionnaire-Revised (CFQ-R) respiratory domain (RD) score from baseline through Week 8 for the VX-445/TEZ/IVA group
- Absolute change in CFQ-R RD score from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry

Exploratory Endpoints

- Absolute change in CFQ-R non-RD scores from baseline through Week 8
- Absolute change in body mass index (BMI) from baseline at Week 8
- Inflammatory mediators
- Blood biomarkers

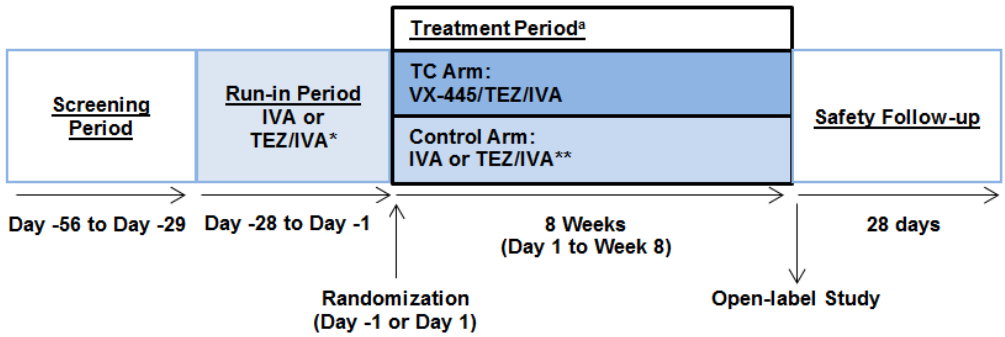
Number of Subjects	Approximately 250 subjects will be enrolled in the study: • Approximately 40% of total subjects will be in the IVA comparator group (approximately 100 subjects) ○ In the IVA comparator group, up to 20% of subjects may be enrolled with an *R117H* mutation (approximately 20 subjects) • Up to 15% of total subjects may be enrolled with SwCl values <30 mmol/L at screening (approximately 40 subjects) Subjects will be randomized (1:1) to the VX-445/TEZ/IVA treatment arm or the control arm (IVA or TEZ/IVA).
Study Population	Male and female CF subjects 12 years of age or older with F/G and F/RF genotypes
Investigational Drug	During the Run-in Period, study drug refers to TEZ/IVA and IVA, as applicable. During the Treatment Period, study drug refers to VX-445/TEZ/IVA and matching placebo, TEZ/IVA and matching placebo, and IVA and matching placebo, as applicable. Active study drugs will be orally administered as fixed-dose combination (FDC) film-coated tablets of VX-445/TEZ/IVA or TEZ/IVA and film-coated IVA tablets. **Active substance:** VX-445/TEZ/IVA **Activity:** VX-445 is a CFTR corrector, TEZ is a CFTR corrector, and IVA is a CFTR potentiator (increased Cl^- secretion) **Strength:** 100 mg/50 mg/75 mg FDC tablet **Active substance:** TEZ/IVA **Activity:** CFTR corrector and CFTR potentiator (increased Cl^- secretion) **Strength:** 100 mg/150 mg FDC tablet **Active substance:** IVA **Activity:** CFTR potentiator (increased Cl^- secretion) **Strength:** 150 mg tablet
Study Duration	The total study duration is approximately 20 weeks (4 weeks for the Screening Period, 4 weeks for the Run-in Period, 8 weeks for the Treatment Period, and 4 weeks for the Safety Follow-up Period).
Study Design	This is a Phase 3, randomized, double-blind, active-controlled, parallel-group, multicenter study (Figure 2-1). In the Run-in Period, subjects will be assigned to the IVA or TEZ/IVA comparator group based on genotype. Subjects assigned to the IVA comparator group will receive IVA 150 mg every 12 hours (q12h) and subjects assigned to the TEZ/IVA comparator group will receive TEZ 100 mg once daily (qd)/IVA 150 mg q12h (Table 2-1). In the Treatment Period, subjects will be randomized (1:1) to the VX-445/TEZ/IVA treatment arm or control arm under a single randomization scheme. Subjects in the control arm who received IVA in the Run-in Period will receive IVA in the Treatment Period; subjects in the control arm who received TEZ/IVA in the Run-in Period will receive TEZ/IVA in the Treatment Period. Randomization will be stratified based on comparator group (IVA comparator versus TEZ/IVA comparator), $ppFEV_1$ as determined during the Run-in Period (Day -14 assessment; <70 versus ≥70), and SwCl as determined during the Run-in Period (Day -14 assessment; <30 mmol/L versus ≥30 mmol/L).

Table 2-1 Treatment Groups and Dosages

Comparator Group	Treatment Arm	VX-445 Dosage	TEZ Dosage	IVA Dosage
IVA	VX-445/TEZ/IVA	200 mg qd	100 mg qd	150 mg q12h
	Control	0 mg	0 mg	150 mg q12h
TEZ/IVA	VX-445/TEZ/IVA	200 mg qd	100 mg qd	150 mg q12h
	Control	0 mg	100 mg qd	150 mg q12h

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

Figure 2-1 VX18-445-104 Study Design



IVA: ivacaftor; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TC: triple combination; TEZ: tezacaftor

Note: The Safety Follow-up Visit is not required for subjects who complete the Week 8 Visit and enroll in an open-label study within 28 days after the last dose of study drug.

[a] Subjects will be randomized 1:1 to the TC arm or the control arm. Randomization will be stratified based on comparator group (IVA comparator versus TEZ/IVA comparator), $ppFEV_1$ as determined during the Run-in Period (Day -14 assessment; <70 versus ≥70), and SwCl as determined during the Run-in Period (Day -14 assessment; <30 mmol/L versus ≥30 mmol/L).

Assessments

Efficacy: Spirometry and CFQ-R

PD: SwCl

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

Pharmacokinetics (PK): VX-445, TEZ, M1-TEZ, and IVA plasma concentrations

Exploratory: DNA sample (optional), inflammatory mediators, blood biomarker samples, and sputum samples

Statistical Analyses

Approximately 250 subjects will be enrolled and randomized (1:1) to the VX-445/TEZ/IVA treatment arm or control arm (IVA or TEZ/IVA).

The primary efficacy endpoint is the absolute change in $ppFEV_1$ from baseline through Week 8

for the VX-445/TEZ/IVA group. The primary null hypothesis to be tested is that the mean absolute change in $ppFEV_1$ from baseline through Week 8 is 0 for the VX-445/TEZ/IVA treatment group. The null hypothesis will be tested at a 2-sided significance level of 0.05.

For the primary hypothesis, assuming a within-group SD of 7.0 percentage points and a 10% dropout rate at Week 8, a sample size of 125 subjects in the VX-445/TEZ/IVA arm will have >99% power to detect the within-group difference of 3.0 percentage points (1 sample *t*-test at a 2-sided significance level of 0.05).

The primary endpoint will be analyzed using a mixed-effects model for repeated measures (MMRM). The model will include the absolute change from baseline in $ppFEV_1$ at Day 15, Week 4, and Week 8 as the dependent variable; treatment group, visit, and treatment by visit as fixed effects; with continuous baseline $ppFEV_1$, continuous baseline SwCl, and comparator group (IVA comparator versus TEZ/IVA comparator) as covariates; and an unstructured covariance structure for the within-subject errors.

For the primary endpoint, the results obtained from the model will be the estimated within-treatment difference through Week 8 (average of Week 4 and Week 8) for the VX-445/TEZ/IVA group. The same model will be used to estimate between group differences (difference between VX-445/TEZ/IVA and the control group) through Week 8. The adjusted mean with a 2-sided 95% CI and a 2-sided *P* value will be provided for the primary endpoint and second key secondary endpoints.

The safety endpoints include AEs, clinical laboratory values, ECGs, vital signs, and pulse oximetry through completion of study participation. The safety analyses will be descriptive only.

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

3 SCHEDULE OF ASSESSMENTS

Schedules of assessments are in Table 3-1 and Table 3-2.

All visits will be scheduled relative to the Day 1 Visit (first dose of randomized study drug in the Treatment Period). For example, the Week 8 (± 5 days) Visit would occur after 8 weeks of study drug administration in the Treatment Period has been completed.

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

Table 3-1 Study VX18-445-104: Screening

Event/Assessment	Screening Period Day -56 Through Day -29	Comments
ICF and assent (when applicable)	X	
Inclusion and exclusion criteria review	X	Sections 8.1 and 8.2
Demographics	X	Section 11.1
Medical history	X	
CFTR genotype	X	Performed for all subjects (Section 11.6.2). In subjects with an *R117H* mutation, linkage to poly-T tract polymorphisms will also be determined from a second specimen. A subject's screening *CFTR* genotype **must** confirm eligibility before the subject enters the Run-in Period (Section 8.1).
FSH	X	Performed for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea (Section 11.6.2)
Serum pregnancy test (all females)	X	Section 11.6.2
Hematology	X	
Coagulation	X	
Serum chemistry	X	
Urinalysis	X	
Weight and height	X	Measured with shoes off (Section 11.1)
OE	X	Conducted only for subjects who are <18 years of age on the date of informed consent (Section 11.6.6)
Complete physical examination	X	Section 11.6.3
Vital signs	X	Performed after subject has been at rest for at least 5 minutes (Sections 11.6.3, 11.6.4, and 11.6.5)
Pulse oximetry	X	
Standard 12-lead ECG	X	
Spirometry	X	May be performed pre- or post-bronchodilator (Section 11.5.1)
Medications review	X	Section 9.5
Sweat chloride	X	Section 11.3
AEs and SAEs	Continuous from signing of the ICF through completion of study participation	Sections 9.1.7, 13.1.1.3, and 13.1.2.2

AE: adverse events; FSH: follicle-stimulating hormone; ICF: informed consent form; OE: ophthalmologic examination; SAE: serious adverse event

Table 3-2 VX18-445-104: Run-in Period, Treatment Period, and Safety Follow-up Visit

Event/Assessment[a]	Run-in Period (4 Weeks)		Treatment Period (8 Weeks)				ETT Visit[b]	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug (If Applicable)[c]	Comments
	Day -28 ± 1 Day	Day -14 ± 2 Days	Day 1[d]	Day 15 ± 3 Days	Week 4 ± 5 Days	Week 8 ± 5 Days			
Clinic visit	X	X	X	X	X	X	X	X	
Inclusion and exclusion criteria confirmation	X								Section 8
CFQ-R	X		X	X	X	X	X	X	Must be completed before any other assessments at relevant clinic visits (Section 11.5.2).
Weight and height	X		X	X	X	X	X	X	Measured with shoes off. Height will only be collected for subjects ≤21 years of age on the date of informed consent (Section 11.1).
OE								X	For subjects <18 years of age on the date of informed consent, an OE is required during Safety Follow-up only if the subject completed study drug dosing through Week 8 of the Treatment Period (Section 11.6.6)
Physical examination	Abbrev		Complete			Complete	Complete		Section 11.6.3
Pregnancy testing	Urine		Urine		Urine	Urine	Serum	Serum	All female subjects (Section 11.6.2)
Standard 12-lead ECG	X		X	X	X	X	X	X	After subject has rested for at least 5 minutes and before dosing, as applicable (Section 11.6.5)

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

[b] If the subject prematurely discontinues study drug treatment, an ETT Visit should be scheduled as soon as possible after the decision to discontinue treatment. Subjects who prematurely discontinue treatment during the Treatment Period will continue to complete all scheduled study visits for assessments following completion of the ETT Visit (Section 9.1.5).

[c] The Safety Follow-Up Visit is required for all subjects, unless the subject completes the Week 8 Visit and has enrolled in an open-label study within 28 days after the last dose of study drug (Section 9.1.4). If an 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 (Section 9.1.5).

[d] To enter the Treatment Period, conditions for entry (Section 9.1.3) must be satisfied.

Table 3-2 VX18-445-104: Run-in Period, Treatment Period, and Safety Follow-up Visit

Event/Assessment[a]	Run-in Period (4 Weeks)		Treatment Period (8 Weeks)				ETT Visit[b]	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug (If Applicable)[c]	Comments
	Day -28 ± 1 Day	Day -14 ± 2 Days	Day 1[d]	Day 15 ± 3 Days	Week 4 ± 5 Days	Week 8 ± 5 Days			
Vital signs	X		X	X	X	X	X	X	After subject has been at rest for at least 5 minutes and before dosing, as applicable (Sections 11.6.3 and 11.6.4)
Pulse oximetry	X		X	X	X	X	X	X	
Spirometry		X	X	X	X	X	X	X	Must be performed before dosing, and should be performed pre-bronchodilator (Section 11.5.1) at approximately the same time at each visit.
SwCl		X	X	X	X	X	X		Must occur before dosing. At each time point, 2 samples will be collected, 1 from each arm (left and right) (Section 11.3)
Urinalysis	X		X			X	X	X	Section 11.6.2
Hematology	X		X	X	X	X	X	X	Day -28 and Day 1: Blood samples will be collected before the first dose of study drug in each study period (Section 11.6.2)
Coagulation	X		X			X	X	X	
Serum chemistry	X		X	X	X	X	X	X	
PK sampling			X	X	X	X	X		Day 1, Day 15, and Week 4: Predose PK within 60 minutes before dosing (Section 11.2.1) Week 8: Predose PK within 60 minutes before dosing for subjects receiving their first dose of study drug in an open-label study. For other subjects, the blood sample should be collected approximately 12 hours after the evening dose of IVA before the Week 8 Visit (Section 11.2.1)
DNA sample (optional)			X						Section 11.4.1
Inflammatory mediator samples	X		X			X	X		Section 11.4.2

Table 3-2 VX18-445-104: Run-in Period, Treatment Period, and Safety Follow-up Visit

Event/Assessment[a]	Run-in Period (4 Weeks)		Treatment Period (8 Weeks)				ETT Visit[b]	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug (If Applicable)[c]	Comments
	Day -28 ± 1 Day	Day -14 ± 2 Days	Day 1[d]	Day 15 ± 3 Days	Week 4 ± 5 Days	Week 8 ± 5 Days			
Blood biomarker samples	X		X			X	X		Section 11.4.3
Blood sample for RNA	X		X			X	X		
Sputum sample	X		X			X	X		Collected from subjects who can produce a sample spontaneously (Section 11.4.4)
Run-in dosing	Day -28 to evening on Day -1								A subject's screening *CFTR* genotype **must** confirm eligibility before the subject enters the Run-in Period (Section 9.1.2 and Section 11.6.2). Run-in dosing details for each comparator group are provided in Section 9.6.1.
Run-in drug count	X	X	X						Section 10.6
Randomization			X						Randomization may occur on either Day -1 or Day 1, after conditions for entry into the Treatment Period (Section 9.1.3) have been met.
Randomized study drug dosing			Day 1 through evening before the Week 8 Visit						Subjects will be randomized 1:1 to the VX-445 200 mg qd/ TEZ 100 mg qd/IVA 150 mg q12h arm or the control arm (IVA 150 mg q12h or TEZ 100 mg qd/IVA 150 mg q12h, depending on comparator group assignment) (Section 9.6.1).
Randomized study drug count			X	X	X	X	X		Section 10.6
Medications review	Continuous from signing of ICF through completion of study participation								Completion of study participation is defined in Section 9.1.7
Treatments and procedures review	Continuous from signing of ICF through completion of study participation								

Table 3-2 VX18-445-104: Run-in Period, Treatment Period, and Safety Follow-up Visit

Event/Assessment[a]	Run-in Period (4 Weeks)		Treatment Period (8 Weeks)				ETT Visit[b]	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug (If Applicable)[c]	Comments
	Day -28 ± 1 Day	Day -14 ± 2 Days	Day 1[d]	Day 15 ± 3 Days	Week 4 ± 5 Days	Week 8 ± 5 Days			
AEs and SAEs	Continuous from signing of ICF through completion of study participation								Completion of study participation is defined in Section 9.1.7. Refer to Sections 13.1.1.3 and 13.1.2.2 for reporting and documentation of AEs and SAEs.

Abbrev: abbreviated; AE: adverse event; CFQ-R: CF Questionnaire-Revised; ETT: Early Termination of Treatment; ICF: informed consent form; IVA: ivacaftor; OE: ophthalmologic examination; PK: pharmacokinetic; SAE: serious adverse event; SwCl: sweat chloride; TEZ: tezacaftor

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BMI	body mass index
bpm	beats per minute
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator protein
CFTR	CF transmembrane conductance regulator gene
Cl^-	chloride ion
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
ETT	Early Termination of Treatment
EU	European Union
F/F	homozygous for *F508del*
F/G	heterozygous for *F508del* and a gating mutation
F/MF	heterozygous for *F508del* with a second CFTR allele carrying a minimal function mutation that is not responsive to TEZ, IVA, and TEZ/IVA
F/RF	heterozygous for *F508del* and a residual function mutation
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F508del	CFTR protein lacking the phenylalanine normally found at position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
$FEF_{25\%-75\%}$	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
GGT	gamma-glutamyl transferase
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

Abbreviation	Definition
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	Investigational New Drug (application) (US)
IPD	important protocol deviation
IRB	institutional review board
IVA	ivacaftor
IWRS	interactive web response system
LUM	lumacaftor
M1-TEZ	metabolite of TEZ
max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function
min	minimum value
MMRM	mixed-effects model for repeated measures
n	number of subjects
OATP1B1	organic anion transporting polypeptide 1B1
OE	ophthalmological examination
P	probability
PD	pharmacodynamic, pharmacodynamics
PEx	pulmonary exacerbation
P-gp	P-glycoprotein
PK	pharmacokinetic, pharmacokinetics
$ppFEV_1$	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
QTcF	QT interval corrected by Fridericia's formula
RD	respiratory domain
RF	residual function
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

Abbreviation	Definition
t-test	statistical test used when the independent variable is binary and the dependent variable is continuous
ULN	upper limit of normal
US	United States
WHO-DD	World Health Organization Drug-Dictionary

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 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 evaluate the efficacy and safety of VX-445/TEZ/IVA in CF subjects who are heterozygous for *F508del* and a second *CFTR* allele carrying either a gating mutation or a

residual function mutation (F/G and F/RF genotypes). Results from the Phase 1/2 study showed that treatment with VX-445/TEZ/IVA resulted in clinically meaningful improvements in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) and sweat chloride (SwCl) in CF subjects with 1 or 2 copies of the *F508del* mutation, namely those with F/MF and F/F genotypes (for the latter, as compared to their TEZ/IVA baseline). These results suggest that VX-445/TEZ/IVA treatment may result in clinical benefit beyond currently approved standard of care CFTR modulators for CF subjects who have F/G and F/RF genotypes.

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the efficacy of VX-445/TEZ/IVA in CF subjects who are heterozygous for *F508del* and a gating or residual function mutation (F/G and F/RF genotypes)

6.2 Secondary Objectives

- To evaluate the safety of VX-445/TEZ/IVA
- To evaluate the pharmacodynamics (PD) of VX-445/TEZ/IVA

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Absolute change in $ppFEV_1$ from baseline through Week 8 for the VX-445/TEZ/IVA group

7.2 Secondary Endpoints

7.2.1 Key Secondary Endpoints

- Absolute change in SwCl from baseline through Week 8 for the VX-445/TEZ/IVA group
- Absolute change in $ppFEV_1$ from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group
- Absolute change in SwCl from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group

7.2.2 Other Secondary Endpoints

- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain (RD) score from baseline through Week 8 for the VX-445/TEZ/IVA group
- Absolute change in CFQ-R RD score from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry

7.3 Exploratory Endpoints

- Absolute change in CFQ-R non-RD scores from baseline through Week 8
- Absolute change in body mass index (BMI) from baseline at Week 8

- Inflammatory mediators
- Blood biomarkers

8 STUDY POPULATION

Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects receive study drug on Day -28.

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

8.1 Inclusion Criteria

1. Subject (or his or her legally appointed and authorized representative) will sign and date an informed consent form (ICF), and, when appropriate, an assent form.
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Age 12 years or older, at the date of informed consent.
4. Confirmed diagnosis of CF as determined by the investigator.
5. Subject is heterozygous for *F508del* and either a gating or residual function mutation (F/G and F/RF genotypes) and is in a region where their genotype and age group are approved indications for treatment with IVA and/or TEZ/IVA (see Appendix A for qualifying mutations).
6. Forced expiratory volume in 1 second (FEV_1) value ≥40% and ≤90% of predicted mean for age, sex, race, and height (equations of the Global Lung Function Initiative [GLI])[11] at the Screening Visit. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria[12] for acceptability and repeatability.
7. Subjects must be able to produce a valid (quantity-sufficient) sweat sample at screening.
8. Stable CF disease as judged by the investigator.
9. Willing to remain on a stable CF treatment regimen (as defined in Section 9.5) through completion of study participation.

8.2 Exclusion Criteria

1. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This includes, but is not limited to, the following:
   - Clinically significant cirrhosis with or without portal hypertension.
   - Solid organ or hematological transplantation.
   - Alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.
   - Cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (each being disease-free for the last 5 years).
2. Any of the following abnormal laboratory values at screening.

- Hemoglobin <10 g/dL
- Total bilirubin ≥2 × upper limit of normal (ULN)
- Aspartate transaminase (AST), alanine transaminase (ALT), or gamma-glutamyl transferase (GGT) ≥3 × ULN
- Abnormal renal function defined as estimated glomerular filtration rate ≤50 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease Study Equation)[13,14] for subjects ≥18 years of age, or ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation)[15] for subjects 12 to 17 years of age (inclusive)

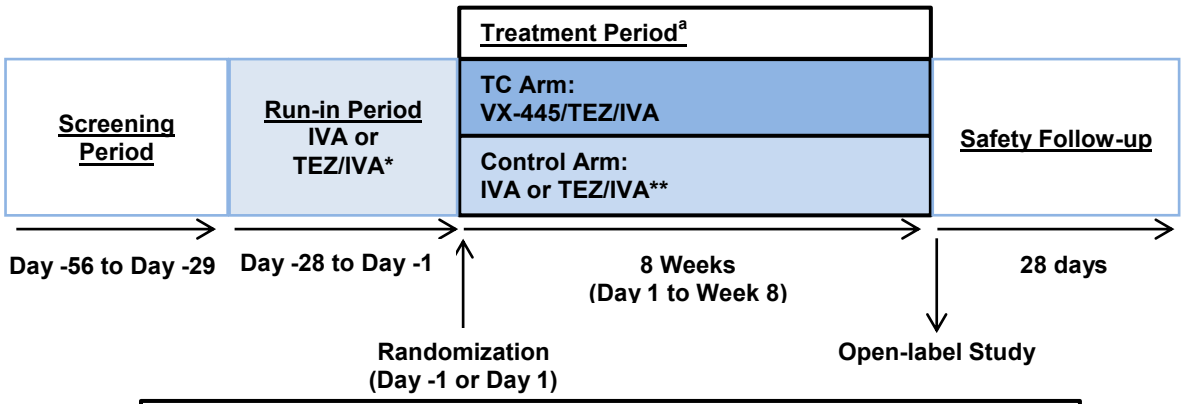
3. An acute upper or lower respiratory infection, pulmonary exacerbation (PEx), or change in therapy (including antibiotics) for sinopulmonary disease within 28 days before the first dose of study drug in the Run-in Period (Day -28).
4. Lung infection with a microbial pathogen that is associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For subjects who have had a history of a positive culture, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
   - The subject has not had respiratory tract culture positive for these organisms within the 12 months before the date of informed consent.
   - The subject has had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent.
5. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug in the Run-in Period (Day -28).
6. Ongoing or prior participation in a study of an investigational treatment other than a Vertex CFTR modulator within 28 days or 5 terminal half-lives (whichever is longer) before screening. The duration of the elapsed time may be longer if required by local regulations.
7. Use of prohibited medications as defined in Table 9-3 within the specified window before the first dose of study drug in the Run-in Period (Day -28).
8. Pregnant or breast-feeding females. All female subjects, regardless of childbearing potential status, must have negative pregnancy tests at the Screening Visit (Day -56) and at the Day -28 Visit, before the first dose of study drug in the Run-in Period.
9. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site. However, an adult (aged 18 years or older) who is a relative of a study staff member may be enrolled in the study provided that
   - the adult lives independently of and does not reside with the study staff member, and
   - the adult participates in the study at a site other than the site at which the family member is employed.

9 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 3, randomized, double-blind, active-controlled, parallel-group, multicenter study (Figure 9-1).

Figure 9-1 VX18-445-104 Study Design



IVA: ivacaftor; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TC: triple combination; TEZ: tezacaftor

Note: The Safety Follow-up Visit is not required for subjects who complete the Week 8 Visit and enroll in an open-label study within 28 days after the last dose of study drug.

[a] Subjects will be randomized 1:1 to the TC arm or the control arm. Randomization will be stratified based on comparator group (IVA comparator versus TEZ/IVA comparator), $ppFEV_1$ as determined during the Run-in Period (Day -14 assessment; <70 versus ≥70), and SwCl as determined during the Run-in Period (Day -14 assessment; <30 mmol/L versus ≥30 mmol/L).

Approximately 250 subjects will be enrolled in the study.

- Approximately 40% of total subjects will be in the IVA comparator group (approximately 100 subjects)
    - In the IVA comparator group, up to 20% of subjects may be enrolled with an *R117H* mutation (approximately 20 subjects)
- Up to 15% of total subjects may be enrolled with SwCl values <30 mmol/L at screening (approximately 40 subjects)

Study drug is defined in Section 10.

In the Run-in Period, subjects will be assigned to the IVA or TEZ/IVA comparator group based on genotype per Table 9-1. Subjects assigned to the IVA comparator group will receive

IVA 150 mg every 12 hours (q12h) and subjects assigned to the TEZ/IVA comparator group will receive TEZ 100 mg once daily (qd)/IVA 150 mg q12h.

In the Treatment Period, subjects will be randomized (1:1) to the VX-445/TEZ/IVA treatment arm or control arm under a single randomization scheme. Subjects in the control arm who received IVA in the Run-in Period will receive IVA in the Treatment Period; subjects in the control arm who received TEZ/IVA in the Run-in Period will receive TEZ/IVA in the Treatment Period.

Randomization will be stratified; details are provided in Section 9.2.

The dosages for the Treatment Period are shown in Table 9-2.

Table 9-1 IVA and TEZ/IVA Comparator Group Mutations

IVA Comparator Group Mutations		
R117H	*G551D*	*G1244E*
G178R	*G551S*	*S1251N*
S549N	*G1069R*	*S1255P*
S549R	*R1070Q*	*G1349D*
TEZ/IVA Comparator Group Mutations		
711+3A>G	*R117C*	*S977F*
2789+5G>A	*E193K*	*F1052V*
3272-26A>G	*L206W*	*K1060T*
3849+10kbC>T	*R347H*	*A1067T*
E56K	*R352Q*	*R1070W*
P67L	*A455E*	*F1074L*
R74W	*D579G*	*D1152H*
D110E	*E831X*	*D1270N*
D110H	*S945L*	

IVA: ivacaftor; TEZ: tezacaftor

Note: This table represents all gating and residual function mutations that may qualify for enrollment in this study but is not intended to determine subject eligibility. Refer to Appendix A for a list of eligible mutations based on approved indications for treatment with IVA and/or TEZ/IVA.

Table 9-2 Treatment Groups and Dosages

Comparator Group	Treatment Arm	VX-445 Dosage	TEZ Dosage	IVA Dosage
IVA	VX-445/TEZ/IVA	200 mg qd	100 mg qd	150 mg q12h
	Control	0 mg	0 mg	150 mg q12h
TEZ/IVA	VX-445/TEZ/IVA	200 mg qd	100 mg qd	150 mg q12h
	Control	0 mg	100 mg qd	150 mg q12h

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

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

9.1.1 Screening

The Screening Period (Day -56 through Day -29) will occur within 28 days before the first dose of study drug in the Run-in Period.

Screening assessments will be used to confirm that subjects meet the eligibility criteria (Table 3-1). The investigator (or an appropriate authorized designee) will obtain informed consent and assent, if applicable, from each subject before any study procedure takes place.

9.1.1.1 Repetition of Screening Assessment(s)

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

9.1.1.2 Rescreening

Subjects who have not entered the Run-in Period may be rescreened once. If a subject is rescreened, all screening assessments will be repeated, except for the following assessments, which are not required to be repeated:

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

If a subject is rescreened, a new screening window will begin when the first rescreening assessment has been initiated.

9.1.1.3 Extension of Screening Period Window

A subject may have the Screening Period window extended by 2 weeks for the following reasons:

- Repetition of the Screening Period assessments (Section 9.1.1.1)
- Unexpected operational or logistic delays, or to meet the eligibility criteria
- Scheduling of OE (for subjects <18 years of age on the date of informed consent, Section 11.6.6)

9.1.2 Run-in Period

The Run-in Period has a 4-week duration and is designed to establish a reliable on-treatment (IVA for the IVA comparator group and TEZ/IVA for the TEZ/IVA comparator group) baseline for the Treatment Period. The first dose of open-label IVA or TEZ/IVA (as applicable) will be administered at the Day -28 Visit. The last dose of open-label IVA will be administered in the evening on Day -1 (1 day before the Day 1 Visit).

A subject's screening *CFTR* genotype **must** confirm eligibility before the subject enters the Run-in Period (Section 11.6.2).

On Day -14, spirometry and SwCl will be assessed. The Day -14 spirometry and SwCl assessments will be used for stratification of randomization (Section 9.2).

Subjects who prematurely discontinue study drug treatment during the Run-in Period will not be randomized or participate in the Treatment Period (Section 9.1.5.1) and are not permitted to rescreen.

9.1.3 Treatment Period

The Treatment Period will be randomized, double-blind, and active-controlled (Table 3-2). It will last approximately 8 weeks (Day 1 to Week 8). Study drug administration details are provided in Section 9.6.

Randomization will occur before the first dose of study drug during the Treatment Period and may occur on either Day -1 or Day 1, after the conditions below have been met. Randomization and stratification details are provided in Section 9.2.

To randomize and enter the Treatment Period, subjects must have stable CF disease (as judged by the investigator) and have remained on a stable CF treatment regimen during the Run-in Period. Female subjects must have a negative pregnancy test at Day 1 before receiving randomized study drug. If these conditions are not met (for example, if the subject has an acute upper or lower respiratory infection, PEx, or changes in therapy [including antibiotics] for sinopulmonary disease during the Run-in Period), the subject will be discontinued and will not be permitted to rescreen.

Subjects who prematurely discontinue study drug treatment during the Treatment Period will remain in the study from the time of discontinuation of study drug treatment through the last scheduled study visit and complete the assessments for all study visits, as described in Section 9.1.5.2.

9.1.4 Safety Follow-up

The Safety Follow-up Visit will occur approximately 28 days after the last dose of study drug for subjects who complete study drug dosing and for subjects who prematurely discontinue study drug dosing, as described in Section 9.1.5 (Table 3-2).

An open-label study will be available for subjects who complete the Week 8 Visit and are eligible. The Safety Follow-up Visit is not required for subjects who complete the Week 8 Visit and enroll in an open-label study within 28 days after the last dose of study drug.

9.1.5 Early Termination of Treatment

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

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

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

9.1.5.1 Discontinuation During the Run-in Period

Subjects who prematurely discontinue study drug treatment during the Run-in Period will not be randomized or participate in the Treatment Period (Section 9.1.3). These subjects will complete

an ETT Visit and Safety Follow-up Visit (as applicable; see Section 9.1.5). The Safety Follow-up Visit will be their last visit in this study.

9.1.5.2 Discontinuation During the Treatment Period

Subjects who prematurely discontinue study drug treatment during the Treatment Period will continue to complete all scheduled study visits for assessments following completion of the ETT Visit, as detailed in Table 3-2. These subjects will complete an ETT Visit and Safety Follow-up Visit (as applicable; see Section 9.1.5).

9.1.6 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.

9.1.7 Completion of Study Participation

Completion of study participation for each individual subject is defined as 1 of the following:

- For subjects who complete the Treatment Period and enter an open-label study within 28 days after the Week 8 Visit: the Week 8 Visit
- For subjects who complete the Treatment Period and do not enter an open-label study within 28 days after the Week 8 Visit: the Safety Follow-up Visit
- For subjects who prematurely discontinue study drug treatment during the Treatment Period but do not withdraw consent (and assent, as applicable): the latest of the Week 8 Visit, ETT Visit, or Safety Follow-up Visit (if required)
- For subjects who prematurely discontinue study drug treatment during the Run-in Period but do not withdraw consent (and assent, as applicable): the ETT or Safety Follow-up Visit (if required)
- For subjects who withdraw consent or assent: date of withdrawal of consent or assent, whichever is earlier (Section 9.9)

If subjects are lost to follow-up (Section 9.1.6), the date of completion of study participation will be defined as the date of the last contact.

The end of study is defined in Section 13.2.8.

9.1.8 Independent Data Monitoring Committee

This study will be monitored by an independent data monitoring committee (IDMC), which will conduct periodic safety reviews of study data (Section 12.3.6.2). Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be included in the IDMC charter. The IDMC charter will be finalized before the first subject is screened.

9.2 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized (1:1) to the VX-445/TEZ/IVA treatment arm or the control arm (IVA or TEZ/IVA).

Randomization will be stratified based on comparator group (IVA comparator versus TEZ/IVA comparator), $ppFEV_1$ as determined during the Run-in Period (Day -14 assessment; <70 versus ≥70), and SwCl as determined during the Run-in Period (Day -14 assessment; <30 mmol/L versus ≥30 mmol/L). If the Day -14 $ppFEV_1$ or SwCl value(s) are not valid or not available, the most recent available valid value(s) will be used for stratification.

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

9.3 Rationale for Study Elements

9.3.1 Study Design

This Phase 3 study will assess the efficacy, PD, and safety of VX-445/TEZ/IVA therapy in CF subjects with F/G or F/RF genotypes.

A randomized, double-blind, active-controlled study design has been selected to ascertain the effects of VX-445/TEZ/IVA while avoiding observer bias. IVA and TEZ/IVA are appropriate active controls because IVA is approved standard of care for treatment of patients with F/G genotypes and selected F/RF genotypes in some regions, and TEZ/IVA is approved for treatment of patients with selected F/RF genotypes in some regions. Subjects will be assigned to a comparator group per Table 9-1.

To establish a reliable on-treatment (IVA or TEZ/IVA) baseline for comparison during the Treatment Period, a 4-week Run-in Period has been incorporated into the study design.

The study has an 8-week treatment duration. Based on prior experience with approved CFTR modulators, 8 weeks is sufficient to assess the impact of TC on the endpoints being evaluated.

Randomization will be stratified by comparator group (IVA comparator versus TEZ/IVA comparator) (Table 9-1) and the subject's $ppFEV_1$ (an index of disease severity) and SwCl values determined at the Day -14 Visit.

9.3.2 Study Population

This study will enroll CF subjects with F/G or F/RF genotypes in regions where their genotype and age group are approved indications for treatment with IVA and/or TEZ/IVA. As described in Section 5.2, treatment with VX-445/TEZ/IVA offers the potential for additional clinical benefit in these subjects, as compared to the standard of care CFTR modulator regimens that are currently approved for these genotype groups.

Given the progressive nature of CF, there is a strong rationale for treating patients earlier in life. Experience with CFTR modulators in adolescent subjects ≥12 to <18 years of age, including with TEZ/IVA, suggests that the exposures and safety profile of VX-445/TEZ/IVA will be similar in adolescents and adults, which supports evaluation of VX-445/TEZ/IVA in adolescents in the present study. Adolescent subjects are currently being evaluated in ongoing Phase 3 studies (Study VX17-445-102 [Study 102] for F/MF subjects, Study VX17- 445-103 [Study 103]

for F/F subjects, and open-label Study VX17-445-105 [Study 105] for both F/MF and F/F subjects).

9.3.3 Study Drug Dose

VX-445 Dosage

A VX-445 dose of 200 mg qd will be administered. This is the dosing regimen that was evaluated in the Phase 3 pivotal studies of VX-445/TEZ/IVA in CF subjects with F/MF and F/F genotypes.

TEZ and IVA Dosages

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

Dosage for Subjects Aged 12 to 17 Years

Phase 3 studies with IVA and TEZ/IVA have demonstrated similar exposures between adults (≥18 years old) and adolescent subjects ≥12 to <18 years of age. In Studies 102 and 103, adolescent subjects in the F/MF and F/F genotype groups are being evaluated at the same dose as adult subjects because VX-445, TEZ, and IVA exposures are expected to be similar in adolescent subjects and adults. Therefore, in the current study, all subjects (both adolescents and adults) will receive the same dose of VX-445/TEZ/IVA.

9.3.4 Rationale for Study Assessments

The safety, pharmacokinetic (PK), 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 CF subjects. Additional exploratory assessments will be obtained to explore inflammatory mediators and other biomarkers.

9.4 Study Restrictions

9.4.1 Prohibited Medications

Table 9-3 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 9-3 Prohibited Medications

Medication	Timing of Restriction: Start of Restriction	Timing of Restriction: End of Restriction	Rationale
Moderate and strong CYP3A inducers	None allowed after the first dose of study drug on Day -28	None allowed through completion of study participation	VX-445, TEZ, and IVA are metabolized extensively via CYP3A4. Therefore, use of moderate and strong inducers and 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 after the first dose of study drug on Day -28	None allowed through completion of study participation	
Non-Vertex CFTR modulators (investigational or approved)	None allowed within 28 days or 5 terminal half-lives (whichever is longer) before screening	None allowed through completion of study participation	These agents may confound the results of this study.
Vertex CFTR modulators (investigational or approved), except for study drugs	None allowed from the first dose of study drug on Day -28	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 from each subject's source documentation for medications taken within 56 days before the Screening Visit through completion of study participation, as defined in Section 9.1.7. Medications will be categorized as defined in Section 12.3.2.3.

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

- Subjects should remain on a stable treatment regimen for their CF from 28 days before the Day -28 Visit through completion of study participation. Stable treatment regimen is defined as the current treatment regimen for CF that subjects have been following for at least 28 days before the Day -28 Visit. Subjects who are on Vertex CFTR modulators (investigational or approved) at the date of informed consent may remain on these during the Screening Period and should transition directly to study drug at the beginning of the Run-in Period on Day -28 without a washout (Table 9-3). Subjects should not initiate long-term treatment with new medication from 28 days before the Day -28 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. The timing of the first dose of study drug on the Day 1 Visit should be synchronized as closely as possible (e.g., not more than ± 3 days) to the first day in the cycle onto the inhaled antibiotic.
- Subjects who alternate between 2 different inhaled antibiotics should remain on the same cycling schedule during the study. The timing of the first dose of study drug on the Day 1 Visit should be synchronized as closely as possible (e.g., not more than ± 3 days) to the first day in the cycle onto 1 of the inhaled antibiotics.

- Subjects may receive doses of prednisone or prednisolone of up to 10 mg/day chronically, or up to 60 mg daily for up to 5 days.
- 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 must have their spirometry assessments performed according to the guidelines provided in Section 11.5.1.

9.6 Administration

9.6.1 Dosing

Study drug will be administered orally. All subjects will receive the same number of tablets each day during the Treatment Period to maintain the blind. 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. In the IVA comparator group, study drug in the Run-in Period will be administered as 1 IVA tablet in the morning and 1 IVA tablet in the evening. Study drug in the Treatment Period will be administered as 2 fixed-dose combination (FDC) TC tablets or matching placebo tablets and 1 IVA tablet or matching placebo tablet in the morning, and 1 IVA tablet in the

evening (Table 9-2). For each subject, doses of study drugs should be taken at approximately the same time (± 2 hours) each day.

3. In the TEZ/IVA comparator group, study drug in the Run-in Period will be administered as 1 TEZ/IVA FDC tablet in the morning and 1 IVA tablet in the evening. Study drug in the Treatment Period will be administered as 2 FDC TC tablets or matching placebo tablets and 1 TEZ/IVA FDC tablet or matching placebo tablet in the morning, and 1 IVA tablet in the evening (Table 9-2). For each subject, doses of study drugs should be taken at approximately the same time (± 2 hours) each day.
4. The date, amount taken, and time of study drug administration, including whether food was taken with each dose, will be recorded for the 2 doses before PK sample collection and the dose received on the morning of PK sample collection (if applicable).
5. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. A meal or snack will be provided by the site for the morning dose of study drug.
6. If a subject's scheduled 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 study drug and the morning dose will be administered in the clinic.
   - If the dose in the clinic will be more than 6 hours after the subject's scheduled morning dose, the subject should take the morning dose of study drug at home.
7. 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

No dose modifications for toxicity are allowed. Treatment may be interrupted as outlined in Section 9.8. If any unacceptable toxicity arises, individual subjects will discontinue dosing (Section 9.1.5).

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. The medical monitor should be notified of any plan to discontinue study drug.

9.8.1 Liver Function Tests

The central laboratory will notify the medical monitor of ALT or AST >3 × 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 criterion is met:

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

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

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

testing within 48 to 72 hours), then the study drug must be permanently discontinued, regardless of the presumed etiology.

9.8.2 Rash

Individuals who develop a generalized rash will be monitored closely. Study drug dosing should be interrupted if a subject develops a generalized rash of Grade 3 or higher, or a rash that is considered a serious adverse event (SAE). The investigator will notify the medical monitor of any rash that results in interruption of study drug, is Grade 3 or higher (Section 13.1.1.4), or is an SAE. Investigators should consider additional evaluation including laboratory testing (e.g., complete blood count with differential, liver function test), photographs of the rash, and dermatology consultation. The investigator may consider resumption of study drug if 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. A subject who prematurely terminates study drug treatment will continue to be followed, unless the subject withdraws consent (or assent, when applicable).

In addition, a subject must be discontinued from study drug treatment if the subject meets either of the following criteria, and should return for study assessments as noted in Section 9.1.5.2:

- Meets any of the stopping (discontinuation) criteria (Section 9.8)
- Becomes pregnant (Section 11.6.7.2)

Other criteria that require subjects to be discontinued from study drug treatment are:

- If a subject is identified after randomization as having been enrolled to the incorrect comparator group, the subject must be discontinued from the study.

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 9.1.5), and follow up with the subject regarding any unresolved AEs.

If a 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 ends, and may use the samples and information in the development of the study compounds, for other drugs and diagnostics, in publications and presentations, and for education purposes. If a 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 before the first dose of study drug on Day 1 of the Treatment Period may be replaced.

Subjects who withdraw or are withdrawn for nonsafety reasons during the study drug treatment period(s) may be replaced at Vertex's discretion.

10 STUDY DRUG INFORMATION AND MANAGEMENT

During the Run-in Period, study drug refers to IVA and TEZ/IVA.

During the Treatment Period, study drug refers to VX-445/TEZ/IVA and matching placebo, TEZ/IVA and matching placebo, and IVA and matching placebo.

10.1 Preparation and Dispensing

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

10.2 Packaging and Labeling

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

10.3 Study Drug Supply, Storage, and Handling

VX-445/TEZ/IVA will be supplied as 2 FDC film-coated tablets (100 mg VX-445/50 mg TEZ/75 mg IVA). Matching VX-445/TEZ/IVA placebo tablets will be of similar size and appearance and contain 0 mg VX-445, 0 mg TEZ, and 0 mg IVA (Table 10-1).

TEZ/IVA will be supplied as an FDC film-coated tablet (100 mg TEZ/150 mg IVA). A matching TEZ/IVA placebo tablet will be of similar size and appearance and contain 0 mg TEZ and 0 mg IVA (Table 10-1).

IVA (150 mg) will be supplied as a film-coated tablet containing 150 mg IVA. Matching IVA placebo tablets will be of similar size and appearance and contain 0 mg IVA (Table 10-1).

Blister cards must be stored under conditions noted in the Pharmacy Manual. The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for via the drug accountability forms, as instructed by Vertex.

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

Drug Name, Dosing Form, Route	Tablet Strength
VX-445/TEZ/IVA, FDC tablet, oral	
VX-445	100 mg
TEZ	50 mg
IVA	75 mg
VX-445/TEZ/IVA-matching placebo, tablet, oral	0 mg
TEZ/IVA, FDC tablet, oral	
TEZ	100 mg
IVA	150 mg
TEZ/IVA-matching placebo, tablet, oral	0 mg
IVA, tablet, oral	150 mg

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

Drug Name, Dosing Form, Route	Tablet Strength
IVA-matching placebo, tablet, oral	0 mg

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

10.4 Drug Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of (1) study drug received; (2) study drug dispensed to the subjects; and (3) study drug returned by the subjects. Subjects will be instructed to return all used and unused materials associated with the study drug to the site. These materials will be retained at the site according to instructions provided by Vertex or its designee. The study monitor will review study drug records and inventory throughout the study.

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

10.7.1 Blinding

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

Individuals who may be unblinded include only the following:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency

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

Access to Spirometry and SwCl Results:

During the conduct of the study, the Vertex study team will not have access to the spirometry or SwCl results after the first dose of study drug in the Treatment Period.

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

Individual SwCl test results will not be disclosed to the study sites with the exception of the screening and Day -14 Visit values. Subjects and their parents/caregivers/companions should not be informed of study-related spirometry results until Vertex has determined that the study has completed (i.e., clinical study report [CSR] finalization), regardless of whether the subject has prematurely discontinued treatment.

10.7.2 Unblinding

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

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

Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators will use their best judgment as to whether to unblind without first attempting to contact the medical monitor to discuss unblinding. If investigators deem it unnecessary to unblind immediately, they will first attempt to contact the medical monitor to discuss unblinding. If investigators have tried but are unable to reach the medical monitor, they will use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding.

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

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

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

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

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.

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

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

11.2 Pharmacokinetics

11.2.1 Blood Sampling

Blood samples will be collected to determine plasma concentrations of VX-445, TEZ, M1-TEZ, and IVA. These samples may also be used to evaluate metabolites of VX-445 and IVA or additional metabolites of TEZ for further evaluation of the bioanalytical method, or for exploratory analyses that provide information on the metabolic pathways used by or affected by VX-445.

The Day 1, Day 15, and Week 4 predose PK samples should be collected within 60 minutes before dosing. The Week 8 predose PK sample should be collected within 60 minutes before dosing for subjects who are receiving their first dose of study drug in an open-label study on the same day as the Week 8 Visit. For subjects who are not entering an open-label study within 24 hours of the Week 8 Visit, the Week 8 sample should be collected approximately 12 hours after the evening dose of IVA before the Week 8 Visit.

All efforts should be made to obtain the PK samples during this specified window. Samples collected outside of the window will be considered protocol deviations.

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

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

11.2.2 Processing and Handling of Pharmacokinetic Samples

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

11.2.3 Bioanalysis

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

11.3 Pharmacodynamics: Sweat Chloride

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

See Section 10.7.1 for information about access to SwCl results.

11.4 Exploratory Assessments

These data will be used for exploratory purposes. Detailed procedures for the collection, processing, storage, and shipment of samples for exploratory assessments will be provided in a separate document.

11.4.1 Pharmacogenomics

An optional single blood sample (DNA sample) will be collected for potential exploratory evaluation of correlations between DNA markers with PK, PD, treatment response, AEs, and biomarkers related to health and disease, including CF, for subjects who choose to participate in this assessment.

11.4.2 Inflammatory Mediators

Blood samples (inflammatory mediator samples) will be collected at the time points noted in Table 3-2 and tested to assess markers related to inflammation. These markers may include, but are not limited to, C-reactive protein, immunoglobulin G, white blood cell (leukocyte) count, and interleukin-8.

11.4.3 Other Blood Biomarkers

Serum from an inflammatory mediator sample and an additional blood sample for plasma will be collected and banked for potential future exploratory evaluation of other blood biomarkers (e.g., proteins, peptides, lipids, metabolites, etc.) in relation to PK, PD, treatment response, AEs, and various disease manifestations of CF.

A blood sample for RNA isolation will be collected as indicated in Table 3-2 for potential exploratory evaluation of gene signatures associated with various disease manifestations of CF and/or treatment response.

11.4.4 Microbiology and Other Sputum Biomarkers

Sputum samples will be collected at the time points noted in Table 3-2 from subjects who can produce a sample spontaneously, and each sample will be processed and frozen. This will establish a baseline for subjects who continue into an open-label study and allow for evaluation of microbiology analysis and sputum biomarkers (which may include, but are not limited to, qualitative and quantitative bacterial and viral assessments including genomic analyses, analysis of immune cells, inflammatory markers, proteins, peptides, lipids, and endogenous metabolites) in relation to PK, PD, treatment response, AEs, and various disease manifestations of CF.

11.5 Efficacy

11.5.1 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines/European Respiratory Society Guidelines[12] 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.

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

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

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

assessment of the spirometry results will be used for the screening assessment and determination of eligibility.

See Section 10.7.1 for information about access to spirometry results.

The measured spirometric values listed below will be converted to percent predicted values using the standard equations of GLI.[11]

- Forced expiratory volume in 1 second (FEV_1) (L)
- Forced vital capacity (FVC) (L)
- FEV_1/FVC (ratio)
- Forced expiratory flow, midexpiratory phase ($FEF_{25\%-75\%}$) (L/s)

11.5.2 Cystic Fibrosis Questionnaire-Revised

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

Subjects will be asked to complete the CFQ-R in their native language, if validated translations are available.[16, 17] If there is no validated translation available in the subject's native language, the subject will not complete the questionnaire. Copies of the CFQ-R used will be provided in the Study Reference Manual. Validated translations of the CFQ-R, if available, will be provided for participating centers in non-English-speaking countries.[18, 19]

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

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

11.6 Safety

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

For subjects <18 years of age on the date of informed consent, OEs will also be performed at screening (if not done within the preceding 3 months).

11.6.1 Adverse Events

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

11.6.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory, with the exception of the urine pregnancy tests. On Day -28 and Day 1, blood samples will be collected before the first dose of study drug in each study period.

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

[a] If urinalysis results are positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be done, 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 Female Subjects: All female subjects, regardless of childbearing potential status, must have a serum pregnancy test at screening. 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. The urine pregnancy test on Day -28 and Day 1 must be negative before the first dose of study drug in each study period. Additional pregnancy tests may be required according to local regulations and/or requirements.

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

CFTR Genotype (Screening Period Only): *CFTR* genotyping will be performed for all subjects. A subject's screening *CFTR* genotype **must** confirm eligibility before the subject enters the Run-in Period. In subjects with an *R117H* mutation, linkage to poly-T tract polymorphisms will also be determined from a second specimen. Specific instructions will be provided in the Laboratory Manual.

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

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

11.6.3 Physical Examinations and Vital Signs

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

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

The abbreviated physical examination will include an assessment of the following body systems: EENT, cardiovascular system, respiratory system, skin, and abdomen.

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

11.6.4 Pulse Oximetry

Pulse oximetry is a noninvasive measure of oxygen delivery to the tissues and has been correlated with clinical status and lung function. Arterial oxygen saturation by pulse oximetry will be assessed following at least a 5-minute rest and before study drug dosing.

11.6.5 Electrocardiograms

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

- The subject will be instructed to rest for at least 5 minutes before having an ECG.
- The test should be performed in the supine position.

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

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

11.6.6 Ophthalmologic Examination

OEs will be conducted at screening only for subjects who are <18 years of age on the date of informed consent. OEs 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.

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

For subjects <18 years of age on the date of informed consent, an OE is required at the Safety Follow-up Visit only if they completed study drug dosing through Week 8 of the Treatment Period. This examination may be completed up to 28 days before the Safety Follow-up Visit, after the last dose of study drug in the Treatment Period.

Any clinically significant abnormal findings will be reported as AEs.

For subjects who subsequently enroll in an open-label study, follow-up OEs will be performed as per that study's protocol.

11.6.7 Contraception and Pregnancy

The effects of VX-445, 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.

11.6.7.1 Contraception

Contraception requirement for a couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. True abstinence must be practiced from the 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 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

Method	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	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.

11.6.7.2 Pregnancy

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

If a female subject becomes pregnant during study participation, study drug will be permanently discontinued immediately. The investigator will notify the medical monitor and Vertex GPS within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form. Male subjects with female partners who become pregnant during the study must use a male condom to avoid exposure of a potential embryo or fetus to study drug via the seminal fluid.

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

12 STATISTICAL AND ANALYTICAL PLANS

12.1 Sample Size and Power

Approximately 250 subjects will be enrolled and randomized (1:1) to the VX-445/TEZ/IVA treatment arm or control arm (IVA or TEZ/IVA).

The primary efficacy endpoint is the absolute change in $ppFEV_1$ from baseline through Week 8 for the VX-445/TEZ/IVA group. The primary null hypothesis to be tested is that the mean absolute change in $ppFEV_1$ from baseline through Week 8 is 0 for the VX-445/TEZ/IVA treatment group. The null hypothesis will be tested at a 2-sided significance level of 0.05.

For the primary hypothesis, assuming a within-group SD of 7.0 percentage points and a 10% dropout rate at Week 8, a sample size of 125 subjects in the VX-445/TEZ/IVA arm will have >99% power to detect the within-group difference of 3.0 percentage points (1 sample *t*-test at a 2-sided significance level of 0.05).

12.2 Analysis Sets

The following analysis sets are defined: All Subjects Set, Full Analysis Set (FAS), and Safety Set. Additional analysis sets related to the Run-in Period will be defined in the Statistical Analysis Plan (SAP), as appropriate.

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

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

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

12.3 Statistical Analysis

12.3.1 General Considerations

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

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

The **baseline value**, unless otherwise specified, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the Treatment Period (i.e., the Day 1 Visit). For ECGs, baseline will be defined as the most recent pretreatment measurement (or the average of triplicate measurements, if the most recent pretreatment measurement is obtained in triplicate) before the first dose of study drug in the Treatment Period (i.e., the Day 1 Visit).

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

The **Treatment-emergent (TE) Period for the Run-in Period** will be from the first dose date of study drug in the Run-in Period to (1) the first dose date of study drug in the Treatment Period for subjects who complete the Run-in Period and continue to the Treatment Period, or (2) 28 days after the last dose date of study drug in the Run-in Period or to the completion of study participation date, whichever occurs first, for subjects who do not continue to the Treatment Period (e.g., subjects who do not meet the conditions to enter the Treatment Period).

The **TE Period for the Treatment Period** will include the time from the first dose of study drug in the Treatment Period (TC, placebo + TEZ/IVA, or placebo + IVA) to 28 days after the last dose of study drug or to the completion of study participation date (as defined in Section 9.1.7), whichever occurs first.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

The number and percentage of subjects in each disposition category (e.g., randomized, included in the FAS, included in the Safety Set, completed Treatment Period, completed study, prematurely discontinued treatment or study with a breakdown of the reasons for

discontinuation, and entered an open-label study) will be summarized overall and by treatment group.

An additional subject disposition summary related to the Run-in Period will be defined in the SAP, as appropriate.

12.3.2.2 Demographics and Baseline Characteristics

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

The following demographics and baseline characteristics will be summarized overall and by treatment group based on the FAS, and will include (but are not limited to): sex, race, ethnicity, baseline age, baseline weight, baseline height, baseline BMI, baseline $ppFEV_1$, and baseline SwCl.

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

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

12.3.2.3 Prior and Concomitant Medications

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

- **Prior medication**: any medication that was administered during the 56 days before the first dose of study drug in the Treatment Period but not in the Run-in Period. For subjects who discontinue during the Run-in Period and whose first dose of study drug in the Treatment Period therefore does not occur, prior medication will be considered any medication that was administered during the 56 days before the last dose of study drug in the Run-in Period but before the first dose in the Run-in Period.
- **Concomitant medication during the Run-in Period**: medication continued or newly received during the TE Period for the Run-in Period.
- **Concomitant medication during the Treatment Period**: medication continued or newly received during the TE Period for the Treatment Period.
- **Post-treatment medication**: medication continued or newly received after:
  - the TE Period for the Run-in Period if the subject did not receive study drug in the Treatment Period
  - the TE Period for the Treatment Period for subjects who received study drug in the Treatment Period

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

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

12.3.2.4 Study Drug Exposure and Compliance

Study drug exposure and compliance will be summarized for the Treatment Period only.

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

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

In addition, percentage of tablets taken will also be summarized overall and by treatment group based on the FAS, and will be calculated as 100 × [(total number of tablets dispensed for the Treatment Period) – (total number of tablets returned for the Treatment Period)] / (total number of tablets planned to be taken per day × duration of study drug exposure in days for the Treatment Period).

12.3.2.5 Important Protocol Deviations

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

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

12.3.3 Efficacy and Pharmacodynamic Analyses

The primary objective of the study is the evaluation of the efficacy of VX-445/TEZ/IVA. The analysis in this section will be based on the FAS, unless otherwise specified.

12.3.3.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the absolute change in $ppFEV_1$ from baseline through Week 8 for the VX-445/TEZ/IVA group. The primary endpoint will be analyzed using a mixed-effects model for repeated measures (MMRM).The model will include the absolute change from baseline in $ppFEV_1$ at Day 15, Week 4, and Week 8 as the dependent variable; treatment group, visit, and treatment by visit as fixed effects; with continuous baseline $ppFEV_1$, continuous baseline SwCl, and comparator group (IVA comparator versus TEZ/IVA comparator) as covariates; and an unstructured covariance structure for the within-subject errors. The Day 15 Visit will not be included in the estimation of the average treatment effect through Week 8. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the *F* test for fixed effects will be estimated using the Kenward-Roger approximation. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, a reduced compound symmetry covariance structure will be used instead. Conditional on the observed data and covariates, missing data due to treatment or study

discontinuation will be assumed to be missing at random; consequently, no imputation of missing data will be performed.

The primary results obtained from the model will be the estimated within-treatment difference through Week 8 (average of Week 4 and Week 8) for the VX-445/TEZ/IVA group. The adjusted mean with a 2-sided 95% CI and a 2-sided *P* value will be provided. Furthermore, the treatment difference at each post-baseline visit will also be provided, obtained from the model.

Sensitivity analyses for handling missing data will be described in the SAP.

Supportive analyses and subgroup analyses by selected baseline characteristics will also be described in the SAP.

12.3.3.2 Analysis of Key Secondary Efficacy Endpoints

The key secondary endpoints are:

- **Absolute change in SwCl from baseline through Week 8 for the VX-445/TEZ/IVA group:** Analysis of this endpoint will be based on the same MMRM model as the analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits will be included in the model.
- **Absolute change in ppFEV$_1$ from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group:** Analysis of this endpoint will be based on the same MMRM model as the analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits will be included in the model. However, the Day 15 Visit will not be included in the estimation of the average treatment effect through Week 8.
- **Absolute change in SwCl from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group:** Analysis of this endpoint will be based on the same MMRM model as the analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits will be included in the model.

Details will be provided in the SAP.

12.3.3.3 Analysis of Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints include:

- **Absolute change in CFQ-R RD score from baseline through Week 8 for the VX-445/TEZ/IVA group**: Analysis of this endpoint will be based on an MMRM model similar to the analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits will be included in the model. However, the Day 15 Visit will not be included in the estimation of the average treatment effect through Week 8.
- **Absolute change in CFQ-R RD score from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group**: Analysis of this endpoint will be based on an MMRM model similar to the analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits will be included in the model. However, the Day 15 Visit will not be included in the estimation of the average treatment effect through Week 8.

Details will be provided in the SAP.

12.3.3.4 Multiplicity Adjustment

A hierarchical testing procedure will be used to control the overall type I error at an alpha of 0.05 for the primary endpoint and the key secondary endpoints tested. The key secondary endpoints will only be tested at an alpha of 0.05 if the primary endpoint of absolute change in $ppFEV_1$ from baseline through Week 8 for the VX-445/TEZ/IVA group is statistically significant. For a test at any step to be considered statistically significant within the testing hierarchy, it must be statistically significant, and all previous tests (if any) within the hierarchy must be statistically significant at the 0.05 level. The testing order of the key secondary endpoints is as follows:

1. First key secondary endpoint: Absolute change in SwCl from baseline through Week 8 for the VX-445/TEZ/IVA group
2. Second key secondary endpoint: Absolute change in $ppFEV_1$ from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group
3. Third key secondary endpoint: Absolute change in SwCl from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group

12.3.3.5 Analysis of Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include:

- **Absolute change in CFQ-R non-RD scores from baseline through Week 8**: Analysis of this endpoint will be based on an MMRM model similar to the analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits will be included in the model. However, the Day 15 Visit will not be included in the estimation of the average treatment effect through Week 8.
- **Absolute change in BMI from baseline at Week 8**: Analysis of this endpoint will be based on an MMRM model similar to the analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits will be included in the model.

Additional details will be specified in the SAP.

12.3.4 Safety Analysis

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

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

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

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

All safety data will be presented in individual subject data listings, including safety data from the Run-in Period.

12.3.4.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs during the Run-in Period, TEAEs during the Treatment Period, or post-treatment AEs, defined as follows:

- **Pretreatment AE**: any AE that started before the first dose of study drug (TEZ/IVA or IVA) during the Run-in Period
- **TEAE during the Run-in Period**: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug (TEZ/IVA or IVA) through the end of the TE Period for the Run-in Period
- **TEAE during the Treatment Period**: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose of study drug (TC or placebo + TEZ/IVA or placebo + IVA) through the end of the TE Period for the Treatment Period
- **Post-treatment AE**: any AE that worsened (either in severity or seriousness) or that was newly developed after:
    - the TE Period for the Run-in Period if the subject did not receive treatment in the Treatment Period
    - the TE Period for the Treatment Period if the subject received treatment in the Treatment Period

For AEs with missing or partial start dates, if there is no clear evidence that the AEs started before or after study drug treatment, then the AEs will be classified as TEAEs corresponding to the Treatment Period. Unless otherwise specified, TEAE refers to TEAE during the Treatment Period.

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

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Grade 3 and Grade 4 TEAEs
- Serious TEAEs
- TEAEs leading to death
- 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 will be presented in the relationship summaries. In addition, a listing containing individual subject level AE data for all deaths and other serious and significant AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

12.3.4.2 Clinical Laboratory Assessments

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

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

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

12.3.4.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided overall and by treatment group, at each scheduled visit and time point, as applicable, for the following standard 12-lead ECG interval measurements (in msec): RR, PR, QT, and QT corrected for HR (QTcF), QRS duration, and HR (beats per minute [bpm]).

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

Additional ECG analyses may be described in the SAP.

12.3.4.4 Vital Signs

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

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

Additional vital signs analyses may be described in the SAP.

12.3.4.5 Pulse Oximetry

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

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

12.3.4.6 Physical Examination

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

12.3.4.7 Other Safety Analysis

Not applicable

12.3.5 Exploratory Endpoints

12.3.5.1 Analysis of Exploratory Endpoints

Details of other analyses, including inflammatory mediators and blood biomarkers analyses, will be provided in a separate document.

12.3.6 Interim and Independent Data Monitoring Committee Analyses

12.3.6.1 Interim Analysis

Not applicable

12.3.6.2 Independent Data Monitoring Committee Analysis

The IDMC (Section 9.1.8) will conduct safety reviews of study data. Details will be described in the IDMC charter.

12.4 Clinical Pharmacology Analysis

12.4.1 Pharmacokinetic Analysis

PK analysis of VX-445, TEZ, M1-TEZ, and IVA may be performed using nonlinear mixed-effects modeling, as data allow. Descriptive statistics will be used to summarize predose plasma concentrations for all analytes.

A detailed description of the planned PK analysis will be presented in the clinical pharmacology analysis plan.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

Study assessments including laboratory tests, ECGs, physical examinations, and vital signs will be assessed and those deemed to have clinically significant worsening from baseline will be documented as an AE. When possible, a clinical diagnosis for the study assessment will be

provided, rather than the abnormal test result alone (e.g., urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself will be listed as the AE (e.g., bacteria in urine or decreased hemoglobin).

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

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

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

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

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time the ICF is signed until the subject completes study participation, as defined in Section 9.1.7.

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

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

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed July 2018). 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	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.

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

Classification	Definition

AE: adverse event

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 followup)

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 completion of study participation, 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 completion of study participation, the SAE Form will be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

For technical issues related to submitting the form, contact telephone: [redacted]

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. When determining the age of the subject, other study eligibility criteria, and timing of collection applicable assessments, the informed consent will be used as the reference (e.g., age at time of informed consent, date of informed consent, timing of AE collection).

13.2.3 Investigator Compliance

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

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all CRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers, and access to subject names linked to such numbers 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 in the CRFs/SAE Forms and the review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/IEC, may also request access to all study records, including source documentation, for inspection.

For sites participating in the 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.

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. Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure, validated, web-based electronic data capture (EDC) application. Vertex will have read-only access to site-entered clinical data in the EDC application.

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

13.4 Monitoring

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

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

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

13.5 Electronic Data Capture

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

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

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

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

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

13.6 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.[20]

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[21]:

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.

14 REFERENCES

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15 APPENDIX A: ELIGIBLE MUTATIONS FOR SUBJECTS WHO ARE HETEROZYGOUS FOR THE *F508DEL-CFTR* MUTATION AND A GATING OR RESIDUAL FUNCTION MUTATION (F/G AND F/RF GENOTYPES)

As described in Section 8.1, subjects heterozygous for the *F508del* mutation and a gating or residual function mutation (F/G and F/RF genotypes) and in regions where their genotype and age group are approved indications for treatment with IVA and/or TEZ/IVA qualify to be screened for the study.

Qualifying gating and residual function mutations that met these conditions at the time of protocol finalization are presented below. Additional mutations may subsequently qualify under these conditions; investigators should contact the medical monitor with questions about such mutations.

Eligible Mutations		
IVA Comparator Group Mutations		
R117H	*G551D*	*G1244E*
G178R	*G551S*	*S1251N*
S549N	*G1069R*	*S1255P*
S549R	*R1070Q*	*G1349D*
TEZ/IVA Comparator Group Mutations		
711+3A>G	*R117C*	*S977F*
2789+5G>A	*E193K*	*F1052V*
3272-26A>G	*L206W*	*K1060T*
3849+10kbC>T	*R347H*	*A1067T*
E56K	*R352Q*	*R1070W*
P67L	*A455E*	*F1074L*
R74W	*D579G*	*D1152H*
D110E	*E831X*	*D1270N*
D110H	*S945L*	

IVA: ivacaftor; TEZ: tezacaftor

16 PROTOCOL SIGNATURE PAGES

16.1 Sponsor Signature Page

Protocol #: VX18-445-104	Version #: 2.0	Version Date: 02 December 2019
Study Title: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the *F508del* Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes)		

This clinical study protocol has been reviewed and approved by the sponsor.

[redacted]

16.2 Investigator Signature Page

Protocol #: VX18-445-104	Version #: 2.0	Version Date: 02 December 2019
Study Title: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the *F508del* Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes)		

I have read Protocol VX18-445-104, Version 2.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-445, tezacaftor, and ivacaftor and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date

1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol Addendum for Cystic Fibrosis

Cystic Fibrosis Studies for the Following Programs

[redacted]

Elexacaftor/Tezacaftor/Ivacaftor (VX-445/VX-661/VX-770)

[redacted]

Version and Date of Protocol Addendum: Version 2.0, 15 May 2020
Replaces Version 1.0, dated 24 April 2020

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

Summary of Changes to Cystic Fibrosis Clinical Study Protocols

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

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

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

Addendum Version 2.0 summarizes additional measures taken for these ongoing CF clinical studies (see table below) to ensure continued safety. In addition, administrative changes were made to provide clarifications (e.g., changed Addendum 1 to Addendum Version 1.0) and to provide examples of qualified personnel (e.g., personnel from site or qualified health care agency) who may conduct safety assessments, as indicated per protocol, during in-home visits.

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

Protocol Change	Rationale for Change	Study Number
Addendum Version 2.0, dated 15 May 2020		
Assessments Weight and height/length/stature may be assessed by subjects or their caregivers using medical grade scales and stadiometers, as indicated per protocol and per local regulation. Sites and subjects will receive training and guidance as needed on these devices. Subjects or caregivers will provide these measurements to site personnel by telephone or video call. Investigators will review results and contact subjects for follow-up as needed. All data will continue to be retained in the subject's source files.	To allow for collection of key data to assess safety and/or efficacy while maintaining study integrity and the safety of subjects and site personnel. *Addendum 1 allowed for these assessments to be performed by qualified personnel conducting the in-home visits. Addendum 2 allows for these assessments to be performed by subjects or caregivers.*	[redacted] [redacted] [redacted] [redacted] VX18-445-104 [redacted] [redacted] [redacted]

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

Protocol Change	Protocol Change	Protocol Change
Addendum Version 1.0, dated 24 April 2020		
Consenting of Subjects ICFs may be provided electronically or by post mail to subjects (and/or caregivers, as indicated per protocol). The subjects and/or caregivers will review the ICF with an appropriately qualified member of the investigator's team via telephone contact or video call. After this review, subjects and/or caregivers will consent (or assent, if applicable), and/or reconsent verbally and by signing and dating the ICF and returning it to the site via post mail. The signed and dated ICF will then be signed and dated by the investigator. Subjects participating in select studies may have the opportunity to enroll in longterm extension studies. Informed consent (or assent, if applicable), and/or reconsent for subjects (and/or caregivers, as indicated per protocol) may be obtained per the same process described above, as applicable.	To provide alternative methods of obtaining reconsent or consent, as applicable, while ensuring subject safety.	[redacted]
Study Drug Shipping Study drug may be shipped directly from the site to the subject, as applicable, and if permitted by local regulations; subject protected health information will not be released to Vertex. Reconciliation, return, and destruction of study drug will continue to occur at the clinical site as indicated per protocol and in adherence to local regulations.	To ensure subjects can continue treatment with study drug without interruption while ensuring their safety. To clarify that despite these alternative measures, reconciliation, return, and destruction of study drug will remain as indicated per protocol.	VX18-445-104 [redacted]
In-home Visits and/or Telephone Contact Study visits may be conducted as in-home visits by qualified personnel as requested by participating sites on a per-subject basis. In addition, all subjects may be contacted by site personnel by telephone or video call, irrespective of in-home visits.	To provide subjects the opportunity to continue participation in the clinical studies while ensuring their safety by minimizing the risk to COVID-19 exposure through travel.	[redacted]

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

Protocol Change	Protocol Change	Protocol Change
Addendum Version 1.0, dated 24 April 2020		
Safety Assessments and Reporting Safety assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits (e.g., personnel from site or qualified health care agency). These assessments may include the following, as indicated per protocol, and per local regulation: • vital signs • pulse oximetry • height/length/stature • weight • physical examination (complete or abbreviated) • pregnancy test (serum or urine) • urinalysis • blood draws for safety test panels (chemistry, LFT panel, lipid panel, hematology, coagulation). Blood and/or urine samples for safety assessments are analyzed as indicated per protocol for subjects who have in-home visits. Blood and/or urine samples for safety assessments may be collected and analyzed at local laboratories for subjects who do not have in-home visits, but do not complete the assessment at the site. In addition, safety assessents will be evaluated by telephone. These assessments may include the review of the following: • AEs • signs and symptoms/systems for CF • medications • planned or unplanned hospitalizations for CF • study drug administration • outcomes related to PEx • outcomes related to antibiotic treatment Investigators will review results (in-home and telephone) and contact subjects for follow-up as needed. All data will continue to be retained in the subject's source files. Any clinically significant finding (e.g., AE, SAE, laboratory abnormalities) will continue to be reported as indicated per protocol.	To assess the safety and tolerability of the CFTR modulator evaluated in the specific clinical study while ensuring subject safety. These safety assessments will continue to provide safety data while minimizing burden to subjects and site personnel. To clarify that despite these alternative measures, all adverse events and serious adverse events should be reported as indicated per protocol.	[redacted] VX18-445-104 [redacted]

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

Protocol Change	Protocol Change	Protocol Change
Addendum Version 1.0, dated 24 April 2020		
Efficacy and Other Assessments Efficacy and other assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits. These assessments may include the following, as indicated per protocol, and per local regulation. In-home Spirometry Assessment A spirometry device may be provided to subjects for in-home assessments of lung function as indicated per protocol. Sites and subjects will receive training and guidance as needed. Patient Reported Outcome CFQ-R questionnaires may be provided to subjects (electronically or post mail) to be completed at home as indicated per protocol. Subjects will return these questionnaires to the site via post mail. Other Assessments • ECGs • sweat chloride • blood samples for *CFTR* genotype testing, [redacted], PK, FSH, inflammatory mediator, biomarkers, and [redacted] • [redacted]	To be able to assess safety, treatment effectiveness, and quality of life measures of the CFTR modulator evaluated in the specific clinical study while ensuring subject safety.	All Efficacy and Other Assessments [redacted] VX18-445-104 [redacted] Other Outcomes Only [redacted]

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

Protocol Change	Protocol Change	Protocol Change
Addendum Version 1.0, dated 24 April 2020		
Remote Monitoring Vertex has implemented remote monitoring visits where applicable, including remote source data verification, as allowed per local regulations. Remote monitoring will focus on collection of safety data, and data supporting primary and key secondary endpoints.	To allow for review of key data to inform on the safety of subjects receiving treatment. To allow for review of other key data to inform on the objectives of the study while maintaining study integrity and the safety of subjects and site personnel.	[redacted] [redacted] [redacted] [redacted] VX18-445-104 [redacted] [redacted] [redacted]

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