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VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3, Open-label Study Evaluating the Long-term Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis

Vertex Study Number: VX18-445-113

IND Number: 132547

EudraCT Number: 2018-004652-38

Date of Protocol: 08 March 2021 (Version 1.4 US)

Replaces Version 1.0, dated 29 May 2019

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Summary of Changes to the Protocol

The previous version of this protocol (Version 1.0, 29 May 2019) was amended to create the current version (Version 1.4 US, 08 March 2021). The protocol history is provided below.

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.0, 29 May 2019	Original version
Version 1.4 US, 08 March 2021	Current version Protocol amended to include an optional at-home sweat chloride sample collection.

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

Change and Rationale	**Affected Sections**
Added an optional at-home sweat chloride sample collection for approximately 50 subjects.	Section 11.5.1

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

2 PROTOCOL SYNOPSIS

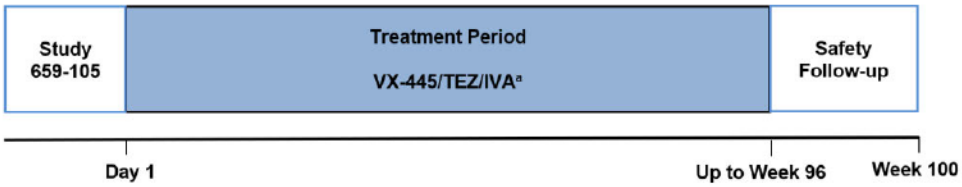
Title	A Phase 3, Open-label Study Evaluating the Long-term Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis
Brief Title	A Study Evaluating the Long-term Safety of VX-445 Combination Therapy
Clinical Phase and Clinical Study Type	Phase 3, safety
Objectives	**Primary Objective** To evaluate the long-term safety and tolerability of VX-445/tezacaftor (TEZ)/ivacaftor (IVA)
Endpoints	**Primary Endpoint** Safety and tolerability of long-term treatment with VX-445/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, pulse oximetry, and spirometry **Other Endpoint** Sweat chloride
Number of Subjects	Over 400 subjects are expected to enroll in this study.
Study Population	Male and female subjects with cystic fibrosis who are 12 years of age or older and homozygous or heterozygous for the *F508del* mutation
Investigational Drug	Study drug refers to VX-445/TEZ/IVA and IVA. Study drugs will be orally administered as 2 fixed-dose combination film-coated tablets (VX-445/TEZ/IVA) in the morning and as 1 film-coated IVA tablet in the evening. **Active substance:** VX-445, TEZ (VX-661), and IVA (VX-770) **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:** IVA (VX-770) **Activity:** CFTR potentiator (increased Cl^- secretion) **Strength:** 150 mg
Study Duration	The total study duration is up to approximately 100 weeks (from the first dose of study drug in this study), including a Treatment Period of up to 96 weeks and a 4-week Safety Follow-up Period.

Study Design

This is a Phase 3, multicenter, open-label study for subjects in Study 659-105, a Phase 3 Vertex study investigating VX-659/TEZ/IVA, who meet eligibility criteria.

All subjects will receive the triple combination of VX-445/TEZ/IVA at the same dose level as that evaluated in the VX-445 Phase 3 pivotal trials.

VX18-445-113 Study Design



IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor
Note: Figure is not drawn to scale.
[a] All subjects will receive VX-445 200 mg qd, TEZ 100 mg qd, and IVA 150 mg q12h.

Assessments

Safety: AEs, clinical laboratory assessments, ECGs, vital signs, height, weight, pulse oximetry, physical examinations, spirometry, and ophthalmologic examinations (the latter for subjects <18 years of age on the date of informed consent in the parent studies of Study 659-105)

Other: Sweat chloride

Statistical Analyses

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

Interim Analyses

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

IDMC Reviews

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

3 SCHEDULE OF ASSESSMENTS

The schedule of assessments is provided in Table 3-1. All visits will be scheduled relative to the Day 1 Visit in this study.

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 VX18-445-113: Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period							ETT Visit[b]	Safety Follow-up Visit (28 ± 7 Days After Last Dose)[c]	Comments
	Day 1[d]	Day 15 (± 3 Days)	Weeks 4, 8, 16, 24, 36 (± 5 Days)	Weeks 12, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92 (± 5 Days)	Week 48 (± 5 Days)	Weeks 60, 72, 84 (± 5 Days)	Week 96 (± 5 Days)			
Clinic visit	X	X	X		X	X	X	X	X	
Telephone contact				X						Results of a home urine pregnancy test will be reported to the site by telephone (Section 11.4.2).
ICF and assent (when applicable)	X									
Inclusion and exclusion criteria confirmation	X									Section 8
Height and weight	X		X		X	X	X	X	X	Measured with shoes off. For subjects whose date of informed consent occurs after their 21st birthday, height will be collected only at the Day 1 Visit (Section 11.4.4).

[a] All assessments will be performed before study drug dosing unless noted otherwise (Section 9.6.1).

[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 (Section 9.1.3).

[c] The Safety Follow-up Visit is required for all subjects unless otherwise specified. Refer to Section 9.1.2 for subjects who transition to a commercially available or managed access program-supplied next-generation corrector TC regimen. For subjects who complete an ETT Visit 3 weeks or later following the last dose of study drug, the ETT Visit will replace the Safety Follow-up Visit (Section 9.1.3).

[d] The Day 1 Visit should occur on the same day as the ETT Visit of Study 659-105 (Section 9.1.1).

Table 3-1 VX18-445-113: Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period							ETT Visit[b]	Safety Follow-up Visit (28 ± 7 Days After Last Dose)[c]	Comments
	Day 1[d]	Day 15 (± 3 Days)	Weeks 4, 8, 16, 24, 36 (± 5 Days)	Weeks 12, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92 (± 5 Days)	Week 48 (± 5 Days)	Weeks 60, 72, 84 (± 5 Days)	Week 96 (± 5 Days)			
Ophthalmologic examination					X		X	X	X	Subjects <18 years of age on the date of informed consent in the parent studies of Study 659-105 will have an ophthalmologic examination within 28 days of the Week 48 and Week 96 Visits. In addition, an ophthalmologic examination will be performed within 28 days of the ETT Visit for subjects who prematurely discontinue study drug if the subject has received at least 12 weeks of study drug since their last ophthalmologic examination. (Section 11.4.7).
Complete physical examination	X						X	X		Section 11.4.3
Pregnancy test	Urine		Urine	Urine	Urine	Urine	Serum	Serum	Serum	All female subjects (Section 11.4.2)
FSH										As needed for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea (Section 11.4.2)
Standard 12-lead ECG	X	X	Weeks 8, 24		X	Week 72	X	X	X	After subjects have rested for at least 5 minutes and before dosing, as applicable (Sections 11.4.3, 11.4.5, and 11.4.6)
Vital signs	X	X	X		X	X	X	X	X	
Pulse oximetry	X	X	X		X	X	X	X	X	
Spirometry	X	X	X		X	X	X	X	X	Section 11.4.8
SwCl			Week 24				X	X		Approximately 50 subjects may participate in 1 to 2 additional, optional sweat tests at unscheduled home visits (Section 11.5.1)
Urinalysis	X				X		X	X	X	Section 11.4.2

Table 3-1 VX18-445-113: Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period							ETT Visit[b]	Safety Follow-up Visit (28 ± 7 Days After Last Dose)[c]	Comments
	Day 1[d]	Day 15 (± 3 Days)	Weeks 4, 8, 16, 24, 36 (± 5 Days)	Weeks 12, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92 (± 5 Days)	Week 48 (± 5 Days)	Weeks 60, 72, 84 (± 5 Days)	Week 96 (± 5 Days)			
Hematology	X	X	X		X	X	X	X	X	
Coagulation	X		Week 24		X	Week 72	X	X	X	
Serum chemistry	X	X	X		X	X	X	X	X	
Study drug count	X	X	X		X	X	X	X		Section 10.6
Study drug dosing	Day 1 through evening before Week 96 Visit									Subjects on study drug interruption from Study 659-105 may NOT begin dosing until they meet the criteria in Section 9.8. Refer to Section 9.6.1 for study drug administration details.
Medications review	Continuous from signing of the ICF (or assent form) through completion of study participation									Completion of study participation is defined in Section 9.1.5.
Treatments and procedures review	Continuous from signing of the ICF (or assent form) through completion of study participation									
AEs and SAEs	Continuous from signing of the ICF (or assent form) through completion of study participation									Completion of study participation is defined in Section 9.1.5. Refer to Section 13.1.2.2 for reporting and documentation of SAEs.

AE: adverse event; ETT: Early Termination of Treatment; FSH: follicle-stimulating hormone; ICF: informed consent form; SAE: serious adverse event; SwCl: sweat chloride

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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
CFTR	CF transmembrane conductance regulator protein
CFTR	CF transmembrane conductance regulator gene
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ECG	electrocardiogram
EDC	electronic data capture
ETT	Early Termination of Treatment
EU	European Union
F508del	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FDA	Food and Drug Administration
FDC	fixed-dose combination
$FEF_{25\%-75\%}$	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
GPS	Global Patient Safety
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	Investigational New Drug (application) (US)
IPD	important protocol deviation
IRB	institutional review board
IVA	ivacaftor
LUM	lumacaftor
max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function
min	minimum value
n	number of subjects

Abbreviation	Definition
OATP	organic anion transporting polypeptide
PE	physical examination
P-gp	P-glycoprotein
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PR	PR interval, segment
PT	Preferred Term
q12h	every 12 hours
qd	once daily
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
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
SwCl	sweat chloride
TC	triple combination
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
ULN	upper limit of normal
US	United States

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 cells derived from 2 groups of patients with CF: 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

The study will provide data on the long-term safety and tolerability of VX-445/TEZ/IVA in subjects with CF who are homozygous or heterozygous for the *F508del* mutation.

Subjects who participated in Study VX17-659-105 and meet eligibility criteria are eligible to enroll. Study 659-105 is an open-label study that enrolled subjects who completed the last Treatment Period visit in a parent study. Parent studies were two Phase 3 pivotal studies investigating VX- 659 in combination with TEZ and IVA. Study VX17-659-102 enrolled F/MF subjects, and Study VX17-659-103 enrolled F/F subjects.

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the long-term safety and tolerability of VX-445/TEZ/IVA

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Safety and tolerability of long-term treatment with VX-445/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, pulse oximetry, and spirometry

7.2 Other Endpoint

Sweat chloride

8 STUDY POPULATION

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

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

8.1 Inclusion Criteria

1. Subject (or his or her legally appointed and authorized representative) is willing to 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. Currently participating in Study 659-105. Current participation is defined as one of the following:
   - On study drug treatment in Study 659-105 as of the day prior to the Day 1 Visit in this study.
   - On study drug interruption in Study 659-105 as of the day prior to the Day 1 Visit in this study.

   Subjects who permanently discontinue VX-659/TEZ/IVA in Study 659-105 for any reason other than enrolling into this study are not eligible.
4. 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 comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.
2. Pregnant and nursing females. All female subjects must have a negative pregnancy test at the Day 1 Visit before receiving the first dose of study drug.
3. History of drug intolerance in Study 659-105 that would pose an additional risk to the subject in the opinion of the investigator (e.g., subjects with a history of allergy or hypersensitivity to VX-659/TEZ/IVA).
4. Current participation in an investigational drug trial (other than Study 659-105). Participation in a noninterventional study (including observational studies, registry studies, and studies requiring blood collections without administration of study drug) and screening for another Vertex study is permitted.

9 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 3, multicenter, open-label study for subjects in Study 659-105, a Phase 3 Vertex study investigating VX-659/TEZ/IVA, who meet eligibility criteria (Section 8).

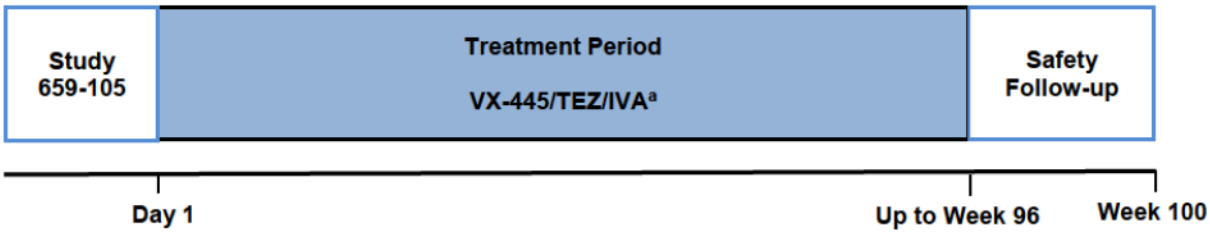
A schematic of the study design is shown in Figure 9-1.

All subjects will receive a TC of VX-445/TEZ/IVA at the same dose level as that evaluated in the VX-445 Phase 3 pivotal trials (VX-445 200 mg qd, TEZ 100 mg once daily [qd], and IVA 150 mg every 12 hours [q12h]). Study drug administration is described in Section 9.6.

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

Study drug is defined in Section 10.

Figure 9-1 VX18-445-113 Study Design



IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor
Note: Figure is not drawn to scale.
[a] All subjects will receive VX-445 200 mg qd, TEZ 100 mg qd, and IVA 150 mg q12h.

9.1.1 Treatment Period

Treatment Period assessments are listed in Table 3-1.

The Day 1 Visit should occur on the same day as the ETT Visit of Study 659-105. Subjects will receive the first dose of study drug on Day 1 after obtaining informed consent (and assent, when

applicable) and confirming eligibility, and completing any pre-dose assessments. Subjects who enroll in this study on a drug interruption will complete Day 1 assessments but will NOT receive the first dose of study drug until they meet the resumption criteria in Section 9.8; before receiving study drug, subjects will repeat all Day 1 assessments (Section 11.4).

Administration details are provided in Section 9.6.

9.1.2 Safety Follow-up

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

The Safety Follow-up Visit is required for all subjects. However, subjects who transition within 28 days of the last dose of study drug to either a commercially available or managed access program-supplied next-generation corrector TC regimen, or to another qualified Vertex study will complete the Week 96 Visit (or the Early Termination of Treatment [ETT] Visit, if the transition occurs before the Week 96 Visit). In these cases, the Week 96 Visit (or the ETT Visit) will replace the Safety Follow-up Visit.

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

9.1.3 Early Termination of Treatment

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

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

During the course of study conduct, if local health authorities decline to approve the TC of VX-445/TEZ/IVA, or if clinical benefit is not demonstrated for the use of the TC for the treatment of CF in specific subpopulations enrolled in this study, subjects with the relevant *CFTR* genotypes may be discontinued after communication to investigators and IRBs/IECs of the risks/benefits related to the safety and efficacy observed for the relevant subset of subjects.

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

9.1.4 Lost to Follow-up

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

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

9.1.5 Completion of Study Participation

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

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

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

The end of study is defined in Section 13.2.8.

9.1.6 Independent Data Monitoring Committee

This study will be monitored by an independent data monitoring committee (IDMC), which will conduct periodic reviews of safety data (Section 12.3.5.2). Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be included in the IDMC charter. The IDMC charter will be finalized before the first subject is enrolled in this study.

9.2 Method of Assigning Subjects to Treatment Groups

This is an open-label study. Randomization is not required because all subjects will be treated identically in a single cohort.

9.3 Rationale for Study Elements

9.3.1 Study Design and Population

This Phase 3 study will enroll subjects who participated in Study 659-105 and meet eligibility criteria. Results from this study will provide information on the long-term safety of TC treatment with VX-445/TEZ/IVA in subjects with CF who are 12 years of age and older and homozygous or heterozygous for the *F508del* mutation, as per the populations enrolled in Study 659-105.

9.3.2 Study Drug Dose and Duration

All subjects will receive a TC of VX-445/TEZ/IVA at the same dosage as that in the VX-445 Phase 3 pivotal trials.

The overall treatment duration will be up to 96 weeks, which is considered sufficient for the evaluation of long-term safety.

9.3.3 Rationale for Study Assessments

All safety assessments are standard parameters for clinical studies in drug development.

9.4 Study Restrictions

9.4.1 Prohibited Medications

Table 9-1 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 9-1 Prohibited Medications

Medication	Timing of Restriction: Start of Restriction	Timing of Restriction: End of Restriction	Rationale
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of study drug	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 within 14 days before the first dose of study drug	None allowed through completion of study participation	
CFTR modulators (investigational or approved), except for study drug and VX-659/TEZ/IVA	None allowed within 28 days or 5 terminal half-lives (whichever is longer) before the first dose of study drug	None allowed until after the last dose of study drug	These agents may confound the results of this study.
CFTR modulators (VX-659/TEZ/IVA)	None allowed after the first dose of study drug (see Section 9.6.1)	None allowed until after the last dose of study drug	These agents may confound the results of this study.

IVA: ivacaftor; TEZ: tezacaftor

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

9.5 Prior and Concomitant Medications

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

- Subjects should remain on a stable treatment regimen for their CF through completion of study participation. Stable treatment regimen is defined as the current treatment regimen for CF that subjects have been following for at least 28 days before Day 1. Subjects should not initiate long-term treatment with new medication from 28 days before the Day 1 Visit through completion of study participation. Subjects who are taking inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
- Subjects may receive doses of prednisone or prednisolone of up to 10 mg/day chronically, or up to 60 mg daily for up to 5 days.
- VX-445 may inhibit organic anion transporting polypeptide (OATP) 1B1 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.

9.6 Administration

9.6.1 Dosing

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

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

1. It is recommended that the dose be taken within 30 minutes of the start of the meal or snack.
2. Study drug will be administered as 2 fixed-dose combination (FDC) VX-445/TEZ/IVA TC tablets in the morning and as 1 IVA tablet in the evening. For each subject, doses of study drug will be taken at approximately the same time (± 2 hours) each day.
3. The last dose of FDC VX-659/TEZ/IVA TC tablets from Study 659-105 should be taken the day prior to the Day 1 Visit for Study 445-113. The first dose of FDC VX-445/TEZ/IVA TC tablets should be administered in the clinic.

   Doses of FDC VX-445/TEZ/IVA TC and FDC VX-659/TEZ/IVA TC should **not** be taken on the same day. If the first dose of FDC VX-445/TEZ/IVA TC tablets is not taken until the afternoon of Day 1, then the subject should skip their evening dose of IVA on Day 1 and subsequently take their second dose of FDC VX-445/TEZ/IVA TC tablets the morning of Day 2 and their first evening dose of IVA the evening of Day 2.

   If the subject inadvertently takes their last dose of FDC VX-659/TEZ/IVA TC tablets from Study 659-105 on the morning of the planned Day 1 Visit for Study 445-113, then the subject should take the first evening dose of IVA on Day 1 and the first dose of FDC VX-445/TEZ/IVA TC tablets the morning of Day 2.
4. On days of scheduled visits, the morning dose of VX-445/TEZ/IVA will be administered at the site after predose assessments have been completed. A meal or snack will be provided by the site for the morning dose of VX-445/TEZ/IVA.

5. If a subject's scheduled visit is to occur in the afternoon, the following guidelines must be used:
   - If the dose in the clinic will be within 6 hours of the subject's scheduled morning dose, the subject should withhold their morning dose of VX-445/TEZ/IVA and the morning dose of VX-445/TEZ/IVA will be administered in the clinic.
   - If the dose in the clinic will be more than 6 hours after the subject's scheduled morning dose of VX-445/TEZ/IVA, the subject should take the morning dose of VX-445/TEZ/IVA at home.
6. Subjects will be instructed to bring all used and unused materials associated with 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 9.9).

9.8 Study Drug Interruption and Stopping Rules

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

The medical monitor should be notified of an interruption of study drug that lasts >72 hours for any reason and of the resumption of study drug after such interruption. In study subjects for whom study drug was previously interrupted, the medical monitor should be notified of any plan to discontinue study drug, before the discontinuation has occurred, if possible.

9.8.1 Liver Function Tests

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

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

If a subject cannot return to the site for confirmatory testing, a local laboratory may be used. Local laboratory results must be reported immediately to the medical monitor, and the subject must have the tests repeated and sent to the central laboratory as soon as possible (ideally within 48 to 72 hours).

Study drug administration **must be interrupted** immediately (prior to confirmatory testing) if any of the following criteria are met:

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

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

Subjects who enroll in this study on a drug interruption because of transaminase elevations in Study 659-105 may NOT receive the first dose of study drug until transaminases return to baseline values from Study 659-105 or ≤2 × ULN, whichever is higher.

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, subjects may receive study drug once transaminases return to baseline from Study 659-105 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 study drug (with confirmation of the initial elevation by repeat testing within 48 to 72 hours), then 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 tests), photographs of the rash, and dermatology consultation. The investigator may consider study drug administration if considered clinically appropriate.

9.9 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons.

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

- Meets any of the stopping (discontinuation) criteria (Section 9.8)
- Becomes pregnant (Section 11.4.9.2)

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for an ETT Visit and Safety Follow-up Visit, if applicable (Section 9.1.2), and follow up with the subject regarding any unresolved AEs.

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

With the exception of subjects who cannot access the commercial product after regulatory approval because reimbursement by the subject's insurance carrier (whether government or private payer) is not yet available or because the subject lacks insurance coverage, subjects who become eligible to receive commercially available VX-445/TEZ/IVA by prescription of a physician may be discontinued from study drug dosing and will complete the ETT Visit before beginning commercially available VX-445/TEZ/IVA dosing. The Safety Follow-up Visit will not be required if the subject immediately continues on commercially available VX-445/TEZ/IVA.

If local health authorities decline to approve VX-445/TEZ/IVA, or if clinical benefit is not demonstrated for the use of VX-445/TEZ/IVA for the treatment of CF in specific subpopulations enrolled in this study, subjects with the relevant *CFTR* genotypes may be discontinued after communication to investigators and IRBs/IECs of the risks/benefits related to the safety and efficacy observed for the relevant subset of subjects.

9.10 Replacement of Subjects

Subjects who withdraw or are withdrawn during the study drug treatment period will not be replaced.

10 STUDY DRUG INFORMATION AND MANAGEMENT

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

10.1 Preparation and Dispensing

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

10.2 Packaging and Labeling

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

10.3 Study Drug Supply, Storage, and Handling

VX-445/TEZ/IVA will be supplied as FDC film-coated tablets containing 100 mg VX-445, 50 mg TEZ, and 75 mg IVA (Table 10-1).

IVA will be supplied as a film-coated tablet containing 150 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 tablets, oral	
VX-445	100 mg
TEZ	50 mg
IVA	75 mg
IVA, tablet, oral	150 mg

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

10.4 Drug Accountability

The pharmacist or designated study site staff will maintain information about the dates and amounts of (1) study drug received; (2) study drug dispensed to the subjects; and (3) study drug returned by the subjects. Subjects will be instructed to return all used and unused materials associated with the study drug to the site. These materials will be retained at the site according to instructions provided by Vertex or its designee. The study monitor will review study drug records and inventory throughout the study. If a site uses a site-specific drug accountability system and/or process, including processes associated with the destruction of returned materials, the process must be documented and approved by Vertex. The study monitor must review the drug accountability documentation on a regular basis. The study monitor will promptly communicate to Vertex any discrepancies he/she is unable to resolve with the site.

10.5 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subjects until the study monitor has performed drug accountability. The investigator will ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Vertex. Destruction will be adequately documented.

10.6 Compliance

To ensure treatment compliance, the investigator or designee will supervise all study drug dosing that occurs at the site. At each visit, site personnel will review that the subject is compliant with study drug dosing and remind the subject of study drug dosing requirements. Compliance will also be assessed by ongoing study drug count.

If a subject demonstrates continued noncompliance of study drug dosing despite educational efforts, the investigator should consider discontinuing the subject from the study.

10.7 Blinding and Unblinding

This will be an open-label study. However, as outlined in Sections 11.4.8 and 11.5.1, subjects (and their parents/caregivers/companions) should not be informed of their study-related spirometry or sweat chloride (SwCl) results until Vertex has determined that the study has been completed (i.e., clinical study report [CSR] finalization). Individual SwCl test results will not be disclosed to the study sites.

11 ASSESSMENTS

The timing of assessments is shown in Section 3 and Table 3-1.

11.1 Subject and Disease Characteristics

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

11.2 Pharmacokinetics

Not applicable.

11.3 Efficacy

Not applicable.

11.4 Safety

Safety evaluations will include AEs, clinical laboratory assessments, and clinical evaluation of ECGs, vital signs, height, weight, pulse oximetry, physical examinations (PEs), spirometry, and ophthalmologic examinations. Ophthalmologic examinations will be conducted only on subjects who were <18 years of age on the date of informed consent in the parent studies of Study 659-105.

11.4.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with ICH GCP Guidelines. Section 13.1 outlines the definitions, collection periods, criteria, and procedures for

documenting, grading, and reporting AEs. A separate document that details AE CRF completion guidelines for investigators as well as training will be provided.

11.4.2 Clinical Laboratory Assessments

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

Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

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

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis[a]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen[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 performed, and results will be provided for leukocytes, erythrocytes, crystals, bacteria, and casts.

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

Pregnancy (beta-human chorionic gonadotropin) Tests: For all female subjects, the urine pregnancy test on Day 1 must be negative before the first dose of study drug. All female subjects must have a pregnancy test every 4 weeks. Serum pregnancy tests will be performed at the study site and analyzed at the central laboratory. Urine pregnancy tests will be performed and analyzed at the site or, at assessment time points when telephone contact takes the place of a clinic visit, at home by using a home kit provided by the site. Results of a home urine pregnancy test will be reported to the site by telephone. Additional pregnancy tests may be required according to local

regulations and/or requirements.

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

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.

11.4.3 Physical Examinations and Vital Signs

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

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

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.

11.4.4 Height and Weight

Height and weight will be measured with shoes off. For subjects whose date of informed consent occurs after their 21st birthday, height will be collected only at the Day 1 Visit. For subjects whose date of informed consent occurs on or before their 21st birthday, height will be collected through the first visit after the subject's 21st birthday and does not need to be collected at future visits.

11.4.5 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.

11.4.6 Electrocardiograms

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

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

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

To ensure 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 (in this study) 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.

11.4.7 Ophthalmologic Examination

Ophthalmologic examinations will be conducted only for subjects who were <18 years of age on the date of informed consent in the parent studies of Study 659-105. The examination does not need to be completed if there is documentation of bilateral lens removal for the subject.

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

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

Subjects <18 years of age on the date of informed consent in the parent studies of Study 659-105 are required to complete a total of 2 ophthalmologic examinations as indicated in Table 3-1. These examinations should be completed within 28 days of the relevant study visit. A single ophthalmologic examination is required at completion of study participation (defined in Section 9.1.5) except for subjects who have withdrawn consent or assent. Ophthalmologic examinations are only required if the cumulative drug exposure (in Study 659-105 and current study) is at least 12 weeks since the last study ophthalmologic examination.

Any clinically significant abnormal findings will be reported as AEs.

11.4.8 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines/European Respiratory Society Guidelines.[11] All sites will be provided with spirometers to be used for all study assessments.

Subjects (and their parents/caregivers/companions) should not be informed of their study-related spirometry results until Vertex has determined that the study has been completed (i.e., CSR finalization), regardless of whether the subject has prematurely discontinued treatment.

The measured spirometric values listed below will be converted to percent predicted values using the standard equations of the Global Lung Function Initiative.[12]

- 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)

11.4.9 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.

11.4.9.1 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

	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.
- 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.

11.4.9.2 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 Global Patient Safety (GPS) within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form. 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.

11.5 Other Assessments

11.5.1 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.

To assess the feasibility of home-based sweat collection, approximately 50 subjects may participate in 1 to 2 additional, optional sweat tests. At this unscheduled home visit, 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.

Subjects (and their parents/caregivers/companions) should not be informed of their study-related SwCl results until Vertex has determined that the study has been completed (i.e., CSR finalization), regardless of whether the subject has prematurely discontinued treatment.

12 STATISTICAL AND ANALYTICAL PLANS

This section presents a summary of the planned analyses for this protocol. Statistical analysis details will be provided in the statistical analysis plan (SAP), which will be finalized before the clinical data lock or before any interim analysis.

12.1 Sample Size and Power

The primary objective of the study is the evaluation of the long-term safety and tolerability of VX-445/TEZ/IVA. This is an open-label study that will enroll subjects who entered the Treatment Period in Study 659-105 and meet eligibility criteria.

Over 400 subjects are expected to enroll in this open-label study of up to approximately 100 weeks duration. With this number of subjects exposed to VX-445/TEZ/IVA treatment, AEs by Preferred Term (PT) that occur with a frequency of >1% will be ruled out with 95% confidence, when 0 events are observed in that PT.

12.2 Analysis Sets

The **All Subjects Set** is defined as all subjects who were enrolled (defined as subject having data in the clinical database) in this study. This analysis set will be used for individual subject data listings and disposition summary tables unless otherwise specified.

The **Safety Set** is defined as all subjects who have received at least 1 dose of study drug in this study. The Safety Set will be used for all safety analyses unless otherwise specified.

12.3 Statistical Analysis

12.3.1 General Considerations

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

place. Any values that require a transformation to standard units (metric or SI) will be converted with the appropriate precision.

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

The baseline value, unless otherwise specified, for the long-term safety analysis will be the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of VX-445/TEZ/IVA in this study. For assessments collected in duplicate or triplicate, the baseline will be defined as the average of non-missing values.

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

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

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

Subject disposition will be summarized for the All Subjects Set. The number and percentage of subjects in the following categories for this study will be summarized as appropriate:

- All Subjects Set
- Dosed (Safety Set)
- Completed Treatment Period
- Prematurely discontinued treatment and the reasons for discontinuation
- Completed study
- Prematurely discontinued the study and the reasons for discontinuation

12.3.2.2 Demographics and Baseline Characteristics

Demographics, background (e.g., medical history), and baseline characteristics will be summarized by descriptive summary statistics.

The following demographics and baseline characteristics will be summarized for the Safety Set and will include (but not limited to) sex, race, ethnicity, baseline age, baseline weight, baseline height, baseline body mass index (BMI), and baseline percent predicted forced expiratory volume in 1 second ($ppFEV_1$).

Medical history will be summarized by MedDRA System Organ Class (SOC) and PT for the Safety Set.

12.3.2.3 Prior and Concomitant Medications

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

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

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

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

12.3.2.4 Study Drug Exposure and Compliance

Study drug exposure will be summarized for the Safety Set in terms of the duration of treatment a subject received in this study, defined as the last day of study drug in this study minus the first day of study drug in this study plus 1, regardless of study drug interruption.

Study drug compliance will be summarized overall based on the Safety Set and will be calculated as: $100 \times [1 - (\text{total number of days of study drug interruption in this study}) / (\text{duration of study drug exposure in days in this study})]$. 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 in this study will also be summarized overall based on the Safety Set and will be calculated as $100 \times [(\text{total number of tablets dispensed in this study}) - (\text{total number of tablets returned in this study})] / (\text{total number of tablets planned to be taken per day} \times \text{duration of study drug exposure in days for this study})$.

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 in this study will be described in the SAP.

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

12.3.3 Safety Analysis

The primary objective of the study is the evaluation of the long-term safety and tolerability of VX-445/TEZ/IVA. All safety analyses will be based on the TE Period in this study for subjects in the Safety Set.

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

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

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

12.3.3.1 Adverse Events

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

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

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

AE summary tables will be presented for TEAEs only and will include the following:

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Serious TEAEs
- TEAEs leading to death
- Grade 3 and Grade 4 TEAEs
- Frequently reported TEAEs

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

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

Exposure-adjusted event rates may also be provided.

12.3.3.2 Clinical Laboratory Assessments

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

The number and percentage of subjects with at least 1 threshold analysis event during the TE Period in this study will be summarized. The shift of the threshold analysis criteria from baseline to post-baseline will also be summarized for selected laboratory parameters. The threshold analysis and parameter selection criteria will be provided in the SAP.

Results of urinalysis and pregnancy tests will be listed in individual subject data listings only. In addition, a listing containing individual subject laboratory assessment values will be provided. This listing will include data from scheduled and unscheduled time points.

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

12.3.3.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided at each time point during the TE Period in this study, for the following standard 12-lead ECG interval measurements (in msec): RR, PR, QT, QTc for heart rate (HR) interval (QTcF), QRS duration, and HR (beats per minute [bpm]).

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

Additional ECG analyses may be described in the SAP.

12.3.3.4 Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized at each time point during the TE Period in this study. 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 in this study will be summarized. The threshold analysis criteria will be provided in the SAP.

Additional vital signs analyses may be described in the SAP.

12.3.3.5 Pulse Oximetry

For the treatment-emergent pulse oximetry measurements, a summary of observed values and change from baseline values will be provided at each time point during the TE Period in this study for the percent of oxygen saturation by pulse oximetry.

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

12.3.3.6 Physical Examination

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

12.3.3.7 Spirometry

Spirometry data (including ppFEV$_1$, FEV$_1$, FVC, FVC/FEV$_1$ ratio, and FEF$_{25\%-75\%}$) will be summarized using descriptive statistics.

12.3.3.8 Other Safety Analyses

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

12.3.4 Other Analyses

Details of other analyses, including sweat chloride, will be included in the SAP.

12.3.5 Interim and Independent Data Monitoring Committee Analyses

12.3.5.1 Interim Analysis

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

12.3.5.2 Independent Data Monitoring Committee Analysis

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

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

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

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

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

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

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

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

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

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time the ICF is signed until the subject completes study participation, as defined in Section 9.1.5.

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. 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.

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 follow-up)

AE: adverse event

13.1.1.8 Treatment Given

The investigator ensures adequate medical care is provided to subjects for any AEs, including clinically significant laboratory values related to study drug. In addition, the investigator will describe whether any treatment was given for the AE. "Yes" is used if any treatment was given in response to an AE, and may include treatments such as other medications, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

An SAE is any AE that meets any of the following outcomes:

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation and is suspected of being a delayed toxicity due to administration of study drug)
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Congenital anomaly or birth defect
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home)

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the subject signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure will not be considered to

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

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

13.1.2.2 Reporting and Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through the subject's 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 the subject's 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: globalpatientsafety@vrtx.com (preferred choice)

Fax: +1-617-341-6159

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

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

13.1.2.3 Expedited Reporting and Investigator Safety Letters

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

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

13.2 Administrative Requirements

13.2.1 Ethical Considerations

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

13.2.2 Subject Information and Informed Consent

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

13.2.3 Investigator Compliance

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

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all 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.[13]

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[14]:

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

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

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

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

13.7.2 Clinical Study Report

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

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX18-445-113	Version #: 1.4 US	Version Date: 08 March 2021
Study Title: A Phase 3, Open-label Study Evaluating the Long-term Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis		

[redacted]

15.2 Investigator Signature Page

Protocol #: VX18-445-113	Version #: 1.4 US	Version Date: 08 March 2021
Study Title: A Phase 3, Open-label Study Evaluating the Long-term Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis		

I have read Protocol VX18-445-113, Version 1.4 US, and agree to conduct the study according to its terms. I understand that all information concerning VX-445, TEZ, and IVA and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date

1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol Addendum for Cystic Fibrosis

Cystic Fibrosis Studies for the Following Programs

[redacted]

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

[redacted]

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

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

Summary of Changes to Cystic Fibrosis Clinical Study Protocols

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

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

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

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

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

Protocol Change	Rationale for Change	Study Number
Addendum Version 3.0, dated 29 July 2020		
Assessments Unscheduled visit(s) will be permissible at the discretion of the investigator(s) or Vertex. The unscheduled visit(s) may be conducted at any time during the study (including after the protocol defined last study visit) in the event assessments specified to be collected at a scheduled visit were not collected due to COVID-19.	To ensure subject safety and/or to facilitate evaluation of safety and/or efficacy if assessments are not performed per the schedule in the protocol due to COVID-19.	[redacted] [redacted] [redacted] [redacted] VX18-445-113 [redacted] [redacted]
Implementaion of measures described in addenda versions 1.0 and 2.0, as applicable.	To ensure subject safety and/or to facilitate evaluation of safety and/or efficacy while maintaining study integrity and the safety of subjects and site personnel.	[redacted]

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[redacted]/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] VX18-445-113 [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.	[redacted] VX18-445-113 [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[redacted]/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 [redacted] 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] VX18-445-113 [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 • [redacted] • blood samples for *CFTR* genotype testing, [redacted] FSH, [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.	[redacted] VX18-445-113 [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] VX18-445-113 [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; [redacted] SAE: serious adverse event; [redacted]