1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-659/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age

Vertex Study Number: VX18-659-106

[redacted]

EudraCT Number: 2018-001711-67

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2 PROTOCOL SYNOPSIS

Title A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-659/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age

Brief Title Evaluation of VX-659/TEZ/IVA in Cystic Fibrosis Subjects 6 Through 11 Years

Clinical Phase and Clinical Study Type Phase 3, pharmacokinetic (PK), safety, and tolerability

Objectives

Part A

Primary Objective

To evaluate the PK of VX-659, tezacaftor (TEZ), and ivacaftor (IVA) when dosed in triple combination (TC)

Secondary Objectives

- To evaluate the PK of TEZ and IVA metabolites
- To evaluate the safety and tolerability of VX-659/TEZ/IVA

[redacted]

Endpoints

Part A

Primary Endpoint

PK parameters of VX-659, TEZ, and IVA, including C_{max}, C_{trough}, and $AUC_{0-\tau}$

Secondary Endpoints

- PK parameters of TEZ and IVA metabolites, including C_{max}, C_{trough}, and $AUC_{0-\tau}$
- Safety and tolerability as determined by adverse events (AEs), clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry

[redacted]

[redacted]

Number of Subjects

Part A

Approximately 12 subjects are planned for enrollment. [redacted]

Study Population

Male and female cystic fibrosis (CF) subjects 6 through 11 years of age who are homozygous for *F508del* (F/F genotype) or heterozygous for *F508del* and a minimal function mutation that is not responsive to TEZ, IVA, or TEZ/IVA (F/MF genotypes). [redacted]

Investigational Drug

Part A

Active substance: VX-659/TEZ/IVA

Activity: CFTR correctors (VX-659 and TEZ) and CFTR potentiator (IVA) (increased chloride ion secretion)

Strength and route of administration: 120-mg VX-659/50-mg TEZ/75-mg IVA fixed-dose combination (FDC) tablet for oral administration **AND** 75-mg IVA tablet for oral administration

Dose administered:

- VX-659 120 mg qd/TEZ 50 mg qd/IVA 75 mg q12h; 1 × VX-659/TEZ/IVA FDC tablet in the morning and 1 × IVA tablet in the evening

[redacted]

[redacted]

Study Duration

Part A

Excluding the Screening Period, subjects will participate in the study for up to 6 weeks (± 7 days)

[redacted]

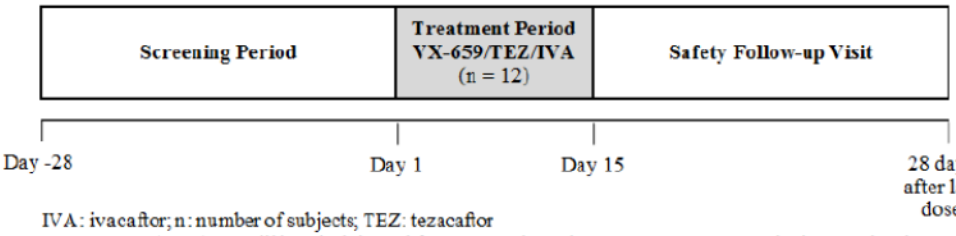
Study Design

This is a Phase 3, 2-part (Parts A [redacted]), multicenter study evaluating the PK, safety, and tolerability of VX-659/TEZ/IVA TC therapy in CF (F/F and F/MF genotypes) subjects 6 through 11 years of age (inclusive).

Part A

A schematic of the study design for Part A is provided below. Approximately 12 subjects (F/F or F/MF genotypes) are planned for enrollment. During the Treatment Period, subjects will be administered VX-659/TEZ/IVA for approximately 15 days. A review of safety, tolerability, and available PK data will be completed by an internal Vertex team after Part A [redacted] Additional subjects may be enrolled as needed in Part A, based on emerging PK data, [redacted]

Part A Study Design



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

[a] VX-659/TEZ/IVA will be administered from Day 1 through Day 15. On Day 15, only the morning dose will be administered.

[redacted]

[redacted]

Parts A [redacted] Doses

Subjects Weight	VX-659 Dose	TEZ Dose	IVA Dose
Part A			
All weights	120 mg qd	50 mg qd	75 mg q12h

[redacted]

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

[redacted]

Assessments

Parts A [redacted]

PK Assessments:

- PK parameters for VX-659, TEZ, and IVA
- PK parameters for TEZ and IVA metabolites

Safety Assessments:

AEs, clinical laboratory assessments (serum chemistry, hematology, coagulation studies, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, ophthalmologic examinations, and physical examinations (PEs)

[redacted]

[redacted]

Statistical Analyses

Data from Parts A [redacted] will be analyzed separately.

Part A

Approximately 12 subjects will be enrolled in Part A. Sample size calculations were determined based on VX-659 PK using noncompartmental analysis-based parameters, such as clearance and volume of distribution. Based on the variability observed in adults, data from 12 subjects will allow 80% power to target a 95% CI within 60% and 140% of the geometric mean estimate of clearance for VX-659.

[redacted]

[redacted]

3 SCHEDULE OF ASSESSMENTS

The schedules of assessments are shown in Table 3-1 (Part A Screening Period), Table 3-2 (Part A Treatment Period and Safety Follow-up Visit), [redacted]

Table 3-1 VX18-659-106, Part A Screening Period

Assessment	Screening Visit (Day -28 to Day -1)	Comments
Informed Consent (and Assent)	X	
Demographics	X	Section 11.1 for details
Medical History	X	Section 11.1 for details
Ophthalmologic Examination	X	Conducted by an ophthalmologist or optometrist (Section 11.5.5)
Full Physical Examination	X	Section 11.5.3 for details
Weight, Height, and BMI	X	Weight and height will be measured with shoes off (Section 11.4.4)
Vital Signs	X	Collected after the subject has been at rest for at least 5 minutes (Section 11.5.3)
Pulse Oximetry	X	Collected after the subject has been at rest for at least 5 minutes (Section 11.5.3)
Standard 12-lead ECG	X	Performed after the subject has been at rest for at least 5 minutes (Section 11.5.4)
Spirometry	X	Performed pre- or post-bronchodilator (Section 11.4.1). Screening spirometry evaluation may be repeated, as specified in (Section 9.1.1.1).
[redacted]		
CF Genotype (all subjects)	X	If the *CFTR* genotype result is not received before the first dose of study drug, a previous *CFTR* genotype laboratory report may be used to establish eligibility (Section 8.1). Subjects who have been enrolled whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).
Serum Pregnancy Test (females of childbearing potential)	X	Females of childbearing potential is defined as females 10 years of age and older (Section 11.5.6)
Serum Chemistry	X	Section 11.5.2 for details
Hematology	X	Section 11.5.2 for details
Coagulation Studies	X	Section 11.5.2 for details
Urinalysis	X	Section 11.5.2 for details
Drug Test (urine only)	X	Section 11.5.2 for details
Alcohol Test (urine only)	X	Section 11.5.2 for details
Inclusion/Exclusion Criteria Review	X	Section 8 for details
Medication Review	X	
AEs and SAEs	X	**Continuous, From Signing of ICF (and Assent Form)**

Table 3-2 VX18-659-106, Part A Treatment Period and Safety Follow-up Visit

Assessment[a]	Day 1	Day 2	Day 4 (± 1 Day)	Day 8 (± 1 Day)	Day 15 (± 1 Day)	ETT Visit	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug	Comments
Clinic Visit	X	X		X	X	X	X	
Telephone Contact			X					
Inclusion and Exclusion Criteria Review	X							Section 8 for details
Safety Assessments								
Full Physical Examination	X				X	X	X	Section 11.5.3 for details. Symptom-directed physical examinations will occur at any time during the study if deemed necessary by the investigator
[redacted]								
Vital Signs	X	X		X	X	X	X	Collected after the subject has been at rest for at least 5 minutes (Section 11.5.3)
Pulse Oximetry	X	X		X	X	X	X	Collected after the subject has been at rest for at least 5 minutes (Section 11.5.3)
Standard 12-lead ECG	X **(triplicate)**	X			X	X	X	Performed after the subject has been at rest for at least 5 minutes and before the AM dose (Section 11.5.4)
[redacted]								
Pregnancy Test (females of childbearing potential)	X **(urine)**				X **(urine)**	X **(urine)**	X **(urine)**	Females of childbearing potential is defined as females 10 years of age and older (Section 11.5.6)
Serum Chemistry	X			X	X	X	X	Section 11.5.2 for details.
Hematology	X			X	X	X	X	Section 11.5.2 for details.
Coagulation Studies	X				X			Section 11.5.2 for details.
Drug Test (urine only)	X							Section 11.5.2 for details.
Alcohol Test (urine only)	X							Section 11.5.2 for details.
Observation 4 hours After the Morning Dose	X							
Concomitant Medications	**Continuous, From Signing of ICF (and Assent Form) Through Completion of Study Participation**							

[a] All assessments will be performed before study drug dosing (within 60 minutes) unless noted otherwise.

Table 3-2 VX18-659-106, Part A Treatment Period and Safety Follow-up Visit

Assessment[a]	Day 1	Day 2	Day 4 (± 1 Day)	Day 8 (± 1 Day)	Day 15 (± 1 Day)	ETT Visit	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug	Comments
Concomitant Treatments and Procedures	**Continuous, From Signing of ICF (and Assent Form) Through Completion of Study Participation**							
AEs and SAEs	**Continuous, From Signing of ICF (and Assent Form) Through Completion of Study Participation**							Section 13.1
PK Assessments								
PK Sampling	X			X	X			**Day 1:** before the AM dose, and at 1, 2, 4, and 6 hours after the AM dose **Day 8:** before the AM dose **Day 15:** before the AM dose, and at 1, 2, 4, and 6 hours after the AM dose If study drug is not administered on the day of the visit (i.e., study drug interruption or permanent discontinuation of study drug), only 1 PK blood sample will be collected. See Table 11-1 for details.
Study Drug Administration								
Meal(s) or Snack(s) at Site	X	X		X	X			Fat-containing food such as a standard "CF" meal or snack will be provided at the site to subjects after all predose assessments have occurred. Section 9.6.1 for details.
VX-659/TEZ/IVA	**Day 1 Through Day 15 (morning dose only on Day 15)**							Administered within approximately 30 minutes of consuming fat-containing food (e.g., standard "CF" meal or snack) (Section 9.6.1). On scheduled visits, the AM dose of study drug will be administered at the site after predose assessments have been completed (food to be provided by site on these days).

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration versus time curve
BMI	body mass index
CF	cystic fibrosis
[redacted]	[redacted]
CFTR	CF transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
CI	confidence interval
Cl^-	chloride ion
C_{max}	maximum observed concentration
CPAP	clinical pharmacology analysis plan
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	predose concentration
CYP	cytochrome P450
[redacted]	[redacted]
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
ETT	Early Termination of Treatment
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F/F	homozygous for *F508del*
F/MF	heterozygous for *F508del* and a minimal CFTR function mutation
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
[redacted]	[redacted]
[redacted]	[redacted]
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
[redacted]	[redacted]
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLI	Global Lung Function Initiative
GPS	Global Patient Safety
HBE	human bronchial epithelial (cells)
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Definition
HR	heart rate
[redacted]	[redacted]
ICF	informed consent form
ICH	International Council for Harmonization
[redacted]	[redacted]
IEC	independent ethics committee
IND	investigational new drug
IRB	institutional review board
[redacted]	[redacted]
IVA	ivacaftor
IWRS	interactive web response system
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
M1-TEZ	metabolite of TEZ
max	maximum value
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal CFTR function mutation
min	minimum value
MMRM	mixed-effects model for repeated measures
N	number of subjects
NCA	noncompartmental analysis
OATP1B1	organic anion transporting polypeptide 1B1
P	probability
PD	pharmacodynamic, pharmacodynamics
PE	physical examination
PK	pharmacokinetic, pharmacokinetics
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PR	PR interval, segment
q12h	every 12 hours
qd	once daily
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTcF	QT interval corrected by Fridericia's formula
[redacted]	[redacted]
RR	interval from the onset of 1 QRS complex to the next
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error

Abbreviation	Definition
SI	SI units (International System of Units)
SUSAR	suspected, unexpected, serious adverse reaction
SwCl	sweat chloride
TC	triple combination
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
ULN	upper limit of normal
US	United States

5 INTRODUCTION

5.1 Background

Cystic fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality and, at present, has no cure. CF affects approximately 70,000 individuals worldwide.[1]

CF is caused by a defect in the gene encoding the CFTR protein, an epithelial chloride (Cl^-) ion channel that is responsible for aiding in the regulation of salt and water absorption and secretion in various tissues.[2] This function is defective in patients with CF due to a loss of cell surface expression and/or function of CFTR. Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is approximately 40 years.[3, 4]

The therapeutic activity of CFTR correctors and potentiators has been established with products that were developed by Vertex and approved for the treatment of CF (Kalydeco® and Orkambi®). Tezacaftor (TEZ; VX-661) is a first-generation CFTR corrector that improves the processing and trafficking of the F508del-CFTR protein, resulting in an increase in the quantity of F508del-CFTR protein at the cell surface. Ivacaftor (IVA) increases the open-channel probability of the F508del-CFTR protein that has been delivered to the cell surface by TEZ, thereby enhancing total chloride transport. The combined effect of TEZ and IVA is increased quantity and function of F508del-CFTR at the cell surface.

VX-659 is a next-generation CFTR corrector. In vitro, the triple combination (TC) of VX-659, TEZ, and IVA (VX-659/TEZ/IVA) increased CFTR chloride transport in *F508del*/*F508del*-human bronchial epithelial (HBE) cells more than any of the dual combinations (VX-659/TEZ, VX-659/IVA, and TEZ/IVA) or individual components (VX-659, TEZ, and IVA) under most conditions studied.[5]

5.2 Study Rationale

Given the progressive nature of CF, there is a strong rationale for treating patients earlier in life. Vertex is currently evaluating VX-659/TEZ/IVA TC therapy in Phase 3 studies in adult and adolescent CF subjects who are heterozygous for *F508del* with a second *CFTR* allele carrying a minimal function (MF) mutation that is not responsive to TEZ, IVA, or TEZ/IVA (F/MF genotypes; Appendix A) and subjects homozygous for *F508del* (F/F genotype). Given the clinical benefit seen in a Phase 2 study of adults with CF with VX-659/TEZ/IVA, the present study is designed to obtain pharmacokinetic (PK), safety, tolerability, and pharmacodynamic (PD) information to expand the evaluation of this study drug in the pediatric population 6 through 11 years of age with F/F or F/MF genotypes (refer to VX-659 Investigator's Brochure).

6 STUDY OBJECTIVES

6.1 Primary Objectives

Part A

To evaluate the PK of VX-659, TEZ, and IVA when dosed in TC

[redacted]

6.2 Secondary Objectives

Part A

- To evaluate the PK of TEZ and IVA metabolites
- To evaluate the safety and tolerability of VX-659/TEZ/IVA

[redacted]

7 STUDY ENDPOINTS

7.1 Primary Endpoints

Part A

PK parameters of VX-659, TEZ, and IVA, including C_{max}, C_{trough}, and $AUC_{0-\tau}$

[redacted]

7.2 Secondary Endpoints

Part A

- PK parameters of TEZ and IVA metabolites, including C_{max}, C_{trough}, and $AUC_{0-\tau}$
- Safety and tolerability as determined by AEs, clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry

[redacted]

8 STUDY POPULATION

Eligibility will be reviewed and documented by a qualified member of the investigator's team before enrollment.

8.1 Inclusion Criteria

Parts A[redacted]

Subjects who meet all of the following inclusion criteria will be eligible for Part A[redacted]

1. Subject (or his or her legally appointed and authorized representative) will sign and date an informed consent form (ICF), and an assent form.
2. Subjects (males and/or females), 6 through 11 years of age, inclusive, on the date of informed consent.
3. Subjects who weigh ≥15 kg without shoes at the Screening Visit.

4. Confirmed diagnosis of CF as determined by the investigator.

5. Subjects who are homozygous for *F508del* (F/F genotype) or heterozygous for *F508del* and a minimal function mutation that is not responsive to TEZ, IVA, or TEZ/IVA (F/MF genotypes; Appendix A).
   - Genotype should be confirmed at the Screening Visit. [redacted]
   - If the screening *CFTR* genotype result is not received before the first dose of study drug, a previous *CFTR* genotype laboratory report may be used to establish eligibility.
   - Subjects who have been enrolled and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).
6. Subjects with FEV_1 ≥40% of predicted normal for age, sex, and height using equations of the Global Lung Function Initiative (GLI)[6] at the Screening Visit (Section 11.4.1).
7. Subjects with stable CF disease as deemed by the investigator at the Screening Visit.
8. Subjects who are willing to remain on a stable CF medication regimen (other than *CFTR* modulators) through Day 15 (**Part A**) [redacted] or, if applicable, through the Safety Follow-up Visit.
9. Subjects who are able to swallow tablets.
10. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit.
11. Subjects of childbearing potential and who are sexually active must meet the contraception requirements outlined in Section 11.5.6.1.
12. As deemed by the investigator, the subject's legally appointed and authorized representative (e.g., parent or legal guardian) AND the subject must be able to understand protocol requirements, restrictions, and instructions. The subject's legally appointed and authorized representative should be able to ensure that the subject will comply with and is likely to complete the study as planned.

8.2 Exclusion Criteria

Parts A [redacted]

Subjects who meet any of the following exclusion criteria will **not** be eligible for Part A [redacted]

1. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This includes, but is not limited to, the following:

- Clinically significant cirrhosis with or without portal hypertension
- Solid organ or hematological transplantation.
- Alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.

- Cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years).

2. Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject (as deemed by the investigator).
3. Any of the following abnormal laboratory values at screening:
   - Hemoglobin <10 g/dL
   - Total bilirubin ≥2 × upper limit of normal (ULN)
   - Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN
   - Abnormal renal function defined as glomerular filtration rate ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation)[7]
4. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug).
5. Lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For subjects who have had a history of a positive culture, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
   - The subject has not had a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent and assent.
   - The subject has had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent and assent.
6. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug (Day 1).
7. A screen positive for drugs of abuse or alcohol, as defined in Section 11.5.2, at the Screening Visit.
8. Ongoing or prior participation in an investigational drug study (including studies investigating VX-659 with or without coadminstration with other study drugs) within 30 days of the Screening Visit.
   - A washout period of 5 terminal half-lives of the previous investigational study drug, or 30 days, whichever is longer, must elapse before the Screening Visit.
   - The duration of the elapsed time may be longer if required by local regulations.

   Note: Ongoing participation in a noninterventional study (including observational studies) is permitted.

9. Use of restricted medication within specified duration before the first dose of study drug as defined in Table 9-2.
10. Female subjects who achieved menarche (had the first menstrual period) who are not willing to follow the contraception requirements outlined in Section 11.5.6.1.
11. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study.

9 STUDY IMPLEMENTATION

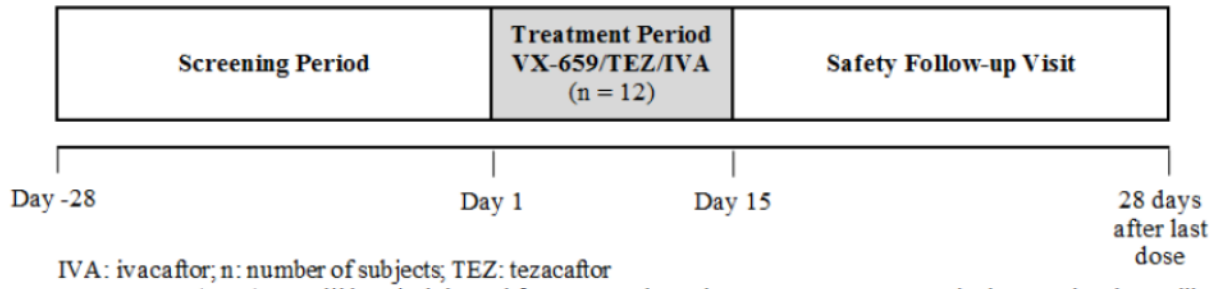
9.1 Study Design

This is a Phase 3, 2-part (Parts A [redacted] multicenter study evaluating the PK, safety, and tolerability of VX-659/TEZ/IVA TC therapy in CF (F/F and F/MF genotypes) subjects 6 through 11 years of age (inclusive).

Part A

A schematic of the study design for Part A is provided below. Approximately 12 subjects (F/F or F/MF genotypes) are planned for enrollment. During the Treatment Period, subjects will be administered VX-659/TEZ/IVA for approximately 15 days. A review of safety, tolerability, and available PK data will be completed by an internal Vertex team after Part A [redacted] Additional subjects may be enrolled as needed in Part A, [redacted]

Figure 9-1 Part A Study Design



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

[a] VX-659/TEZ/IVA will be administered from Day 1 through Day 15. On Day 15, only the morning dose will be administered.

[redacted]

[redacted]

Table 9-1 Parts A [redacted]

Subjects Weight	VX-659 Dose	TEZ Dose	IVA Dose
Part A			
All subjects	120 mg qd	50 mg qd	75 mg q12h
[redacted]			

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

[redacted]

9.1.1 Screening

Parts A [redacted]

Screening will occur within 28 days before administration of study drug. The investigator (or an appropriate authorized designee) will obtain informed consent and assent, if applicable, for each subject before any study procedure takes place.

Subjects previously screened for another Vertex study may participate in this study provided they meet the eligibility criteria (Section 8). Screening data from the previous study will be considered sufficient to satisfy the requirements of this study. Procedures required by this protocol will only be done if the procedures were not performed for the previous study. All

screening data from these subjects must be obtained within 28 days before administration of study drug.

To prepare for study participation, subjects will be instructed on the study restrictions (Section 9.4) and concomitant medications (Section 9.5).

9.1.1.1 Repetition of Screening Assessments

Parts A [redacted]

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

9.1.1.2 Rescreening

Parts A [redacted]

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

- *CFTR* genotyping
- Ophthalmologic examination (if performed within 3 months of the date of informed consent)

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

9.1.1.3 Extension of Screening Period Window

Parts A [redacted]

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

- Repetition of the Screening Period assessments (Section 9.1.1.1)
- Unexpected operational or logistic delays, or to meet the eligibility criteria
- Scheduling of ophthalmologic examination (Section 11.5.5)

9.1.2 Treatment Period

Parts A [redacted]

The Treatment Period will last approximately 15 days in Part A [redacted] Study drug administration details are provided in Section 9.6.

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

[redacted]

9.1.3 Follow-up

Part A

Subjects will have a Safety Follow-up Visit 28 (± 7) days after the last dose of study drug.

[redacted]

9.1.4 Early Termination of Treatment

Parts A [redacted]

If a subject prematurely discontinues study drug treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the decision to discontinue treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit (Table 3-2 for Part A [redacted] if applicable (Section 9.1.3).

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.

[redacted]

9.1.6 Completion of Study Participation

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

Part A

- For subjects who complete the Treatment Period: the Safety Follow-up Visit
- For subjects who prematurely discontinue study drug treatment but do not withdraw consent (and assent, as applicable): the latest of the Day 15 Visit, ETT Visit, or Safety Follow-up Visit
- For subjects who withdraw consent or assent: date of withdrawal of consent or assent, whichever is earlier (Section 9.9)

[redacted]

9.2 Method of Assigning Subjects to Treatment Groups

An interactive web response system (IWRS) will be used.

9.3 Rationale for Study Elements

9.3.1 Study Design

The subjects studied are from the population that is expected to benefit from treatment with VX-659/TEZ/IVA.

Part A

The open-label design is considered adequate to evaluate the PK and safety of VX-659/TEZ/IVA in this pediatric population. [redacted]

9.3.2 Study Population

Parts A [redacted]

Patients with an F/MF genotype (30% of all patients with CF) generally have severe disease and do not have approved CFTR modulator therapy available to them; clinical studies of LUM/IVA and TEZ/IVA did not show improvement in lung function in this patient population. Without an available CFTR modulator therapy, patients with F/MF genotypes must continue to rely on adjunctive treatments and symptomatic therapies to manage their severe CF disease. Although the rate of decline in lung function is reduced in *F508del* homozygous patients treated with Orkambi[8], this population has an inexorable decline in lung function. Based on in vitro data and preliminary clinical data, VX-659/TEZ/IVA is expected to provide a clinically relevant advantage over currently available treatments for F/MF and F/F patients.

Given the progressive nature of CF, there is a strong rationale for treating patients earlier in life. Experience with CFTR modulators in pediatric subjects ≥6 to ≤11 years of age, including with TEZ/IVA, suggests that the safety profile of VX-659/TEZ/IVA will be similar in children and adults, which supports evaluation of VX-659/TEZ/IVA in pediatric subjects in the present study.

9.3.3 Study Drug Dose and Duration

Parts A [redacted]

VX-659 Dosage

A VX-659 dose of 240 mg once daily (qd) is currently under evaluation in ongoing Phase 3 studies of adult and adolescent (≥12 years of age) CF subjects with an F/MF or F/F genotype. The 240 mg dose was selected based on an assessment of the benefit-risk profile from Phase 2 Study VX16-659-101 (Study 659-101), which evaluated a range of VX-659 doses (80 mg qd, 240 mg qd, and 400 mg qd) in TC with TEZ/IVA in subjects with F/MF and F/F genotypes. In Study 659-101, the TC was generally safe and well tolerated in all VX-659 dose groups. Subjects with F/MF genotypes who received the VX-659 240 mg qd TC demonstrated a clinically meaningful improvement in $ppFEV_1$ (within-group mean [SE] absolute change of 11.6 [2.1] percentage points from baseline [$P<0.0001$], compared with a mean absolute change of 0.3 [2.8] percentage points in subjects who received placebo [$P = 0.9053$]). The improvement

in ppFEV$_1$ for VX-659 400 mg qd in TC with TEZ/IVA was similar to improvements for VX-659 240 mg qd.

The VX-659 dose of 120 mg qd selected for evaluation in the current study was determined based on population-PK modeling utilizing data from adults and simulating exposure over a range of body weights typical for a population of 6 to <12 year-olds, ranging from 15 to 50 kg. The simulations indicate that a dose of 120 mg qd is predicted to provide similar exposures to that observed in adults dosed with 240 mg qd, up to a body weight of approximately 40 kg. At a body weight of 40 kg or higher, exposure of VX-659 following dose of 120 mg is predicted to be low relative to that of adults dosed with 240 mg qd. At ≥40 kg, a dose of 240 mg qd is predicted to provide similar exposure to that of adults. A single dose level of 120 mg qd will be evaluated in Part A to confirm the appropriateness of the doses [redacted]

Therefore, the dose selected for evaluation in Part A is predicted to be safe. [redacted]

TEZ and IVA Dosages

TEZ will be administered as 50 mg qd and IVA will be administered as 75 mg every 12 hours (q12h) in all subjects in Part A [redacted]

Part A

Duration of Dosing

The 15-day duration of dosing was chosen to provide an adequate assessment PK, safety, and tolerability of VX-659/TEZ/IVA [redacted]

[redacted]

9.3.4 Rationale for Study Assessments

Parts A [redacted]

The PK, safety, efficacy, and PD assessments are standard parameters for clinical studies in drug development and are generally recognized as reliable, accurate, and relevant to the study of subjects with CF. Ophthalmologic examinations were added to the standard safety assessments.

9.4 Study Restrictions

9.4.1 Prohibited Medications

Parts A [redacted]

To avoid variable study results that may affect various metabolizing enzymes and transporters during in vivo studies (e.g., uncontrolled use of dietary/nutritional supplements), it is important to exclude subjects who do not comply with the study restrictions and prohibited medications summarized in Table 9-2.

Table 9-2 Prohibited Medications

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

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

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

9.4.2 Exposure to Sunlight

Parts A [redacted]

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

9.5 Prior and Concomitant Medications

Parts A [redacted]

Prohibited medications as described in Section 9.4.1 are not allowed in this study while subjects are receiving study drug. A nonexhaustive study prohibitions and cautions list for food and medications will be provided in the Study Reference Manual.

9.6 Administration

9.6.1 Dosing

Part A

On Day 1 through Day 15, VX-659/TEZ/IVA will be orally administered with water. On Day 15, only the morning dose of VX-659/TEZ/IVA will be administered.

Study drug should be administered within approximately 30 minutes of the start of a fat-containing snack or meal, such as a standard "CF" meal or snack according to the following guidelines:

1. Morning dose of study drug will be administered at the site on Days 1, 2, 8, and 15.
2. Study drug will be administered after all predose assessments have been performed.
3. All doses of study drug (morning and evening, as applicable) should be administered at approximately every 12 hours (± 1 hour) on each dosing occasion (e.g., if the morning doses of study drug are administered at 08:00 hour on Day 1, all subsequent morning doses should be administered between 07:00 hour and 09:00 hour).
4. Study drug tablets will be administered within 5 minutes of each other.
5. Study drug will be administered with approximately 240 mL (approximately 1 cup, 8 ounces, or half a pint) of water.
6. At the Day 1 Visit, all subjects will be observed for 4 hours after the morning dose of the study drug.
7. The date, amount taken, and time of study drug administration including whether food was taken with each dose, will be recorded for 2 days before PK sample collection and on the days of PK sample collection.

[redacted]

[redacted]

9.6.2 Missed Doses

9.6.2.1 Morning Dose of Study Drug

Parts A [redacted]

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

9.6.2.2 Evening Dose of Study Drug

Parts A [redacted]

If a subject misses the evening dose of IVA and recalls within 6 hours, the subject should take his/her dose with food. If more than 6 hours have elapsed after his/her usual dosing time, the subject should skip that dose and resume his/her normal schedule for the following dose.

9.7 Dose Modification for Toxicity

Parts A [redacted]

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

9.8 Study Drug Interruption and Stopping Rules

9.8.1 Liver Function Tests

Parts A [redacted]

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

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

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

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

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

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

Study drug administration **must be discontinued** if the following criteria are met:

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

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

If an alternative, reversible cause of transaminase elevation with or without increased bilirubin or clinical jaundice has been identified, study drug administration may be resumed once transaminases return to baseline or are ≤2 × ULN, whichever is higher. Regardless of the duration of interruption, the medical monitor should be notified prior to resumption of study drug. Upon resumption of study drug, transaminases and bilirubin should be assessed weekly for 4 weeks. If a protocol-defined transaminase elevation interruption threshold recurs within 4 weeks of rechallenge with the study drug (with confirmation of the initial elevation by repeat testing within 48 to 72 hours), then the study drug must be permanently discontinued, regardless of the presumed etiology.

9.8.2 Rash

Parts A [redacted]

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 resumption of study drug if considered clinically appropriate.

9.9 Removal of Subjects

Parts A [redacted]

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

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

- Has a screening *CFTR* genotype that does not confirm study eligibility if a previous *CFTR* genotype laboratory report was used to establish eligibility. These subjects must be discontinued from the study (Section 8.1)
- Meets any of the stopping (discontinuation) criteria (Section 9.8)
- Has a QTcF value above the threshold for repeat measurement (Section 11.5.4)
- Becomes pregnant (Section 11.5.6.2)

Subjects who discontinue study drug treatment should return for study assessments, as noted in Section 9.1.4.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for an ETT Visit and Safety

Follow-up Visit, if applicable (see Section 9.1.4), and follow up with the subject regarding any unresolved AEs.

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

9.10 Replacement of Subjects

Part A Only

Subjects who withdraw or are withdrawn for nonsafety reasons during the Treatment Period may be replaced as needed in Part A, [redacted]

10 STUDY DRUG INFORMATION AND MANAGEMENT

Parts A [redacted]

Study drug refers to VX-659/TEZ/IVA.

10.1 Preparation and Dispensing

Parts A [redacted]

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

Parts A [redacted]

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

Parts A [redacted]

Table 10-1 provides the study drug information. The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. Detailed instructions regarding the storage, handling, and dispensation of the study drug will be provided in the Pharmacy Manual.

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

Drug Name, Dosing Form, Route	Strength	[redacted]
	Part A: All Subjects	
VX-659/TEZ/IVA, FDC tablet, oral		
VX-659	120 mg	
TEZ	50 mg	
IVA	75 mg	
IVA, tablet, oral	75 mg	

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

10.4 Drug Accountability

Parts A [redacted]

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

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

10.5 Disposal, Return, or Retention of Unused Drug

Parts A [redacted]

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

Parts A [redacted]

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

Parts A [redacted]

This will be an open-label study; however, subjects and their legally appointed and authorized representative (e.g., parent or legal guardian) should not be informed of their [redacted] results during the Treatment Period, regardless if the subject permanently discontinues treatment.

11 ASSESSMENTS

The timing of assessments is shown in Table 3-1 through Table 3-4.

The following assessments must be performed in the order specified below when more than 1 assessment is required at a particular time point:

Parts A [redacted]

1. Vital signs
2. Pulse oximetry
3. Standard 12-lead ECG recordings
4. Safety laboratory assessments
5. PK sampling [redacted] may be performed in either order when occurring at the same time point. PK blood samples collected before dosing must be collected within 60 minutes before dosing as described in Section 11.2.1.

[redacted]

11.1 Subject and Disease Characteristics

Parts A [redacted]

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

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

11.2 Pharmacokinetics

11.2.1 Blood Sampling

Parts A[redacted]

Blood samples will be collected to determine plasma concentrations of VX-659, TEZ, M1-TEZ, IVA, and M1-IVA. These samples may also be used to evaluate metabolites of VX-659 and additional TEZ and IVA metabolites, for further evaluation of the bioanalytical method, [redacted]

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

Table 11-1 Acceptable Pharmacokinetic Sampling Windows

Sampling Time	Time From Scheduled Sampling Allowed
predose (before morning dose)	within 60 minutes before dosing
>0.25 and <6 hours after morning dose	± 10 minutes
≥6 hours after morning dose	± 30 minutes

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

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

11.2.2 Processing and Handling of Pharmacokinetic Samples

Parts A[redacted]

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

11.2.3 Bioanalysis

Parts A[redacted]

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

[redacted]

11.4 Efficacy

11.4.1 Spirometry

Parts A [redacted]

Spirometry will be performed according to the American Thoracic Society Guidelines[13] and according to the additional guidelines that follow.

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

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

During the Screening Period, spirometry assessments may be performed pre- or post-bronchodilator [redacted]

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

See Section 10.7 for information about access to spirometry results.

The measured spirometric values listed below will be converted to percent predicted values using the standard equations of GLI.[6]

- FEV_1 (L)

[redacted]

[redacted]

11.4.4 Height and Weight

Parts A [redacted]

Height and weight will be measured with shoes off and before the dose of the study drug during the Treatment Period.

[redacted]

11.5 Safety

Parts A [redacted]

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

Medical history and PE information will be collected during the course of the study and will be captured in the source documentation. Physical examinations post-baseline will not be captured for inclusion into the study database. However, any untoward findings identified on PEs conducted after the administration of the first dose of study drug will be captured as an AE if

those findings meet the definition of an AE. Demographic data collected at the Screening Visit will be included in the study database.

11.5.1 Adverse Events

Parts A [redacted]

All AEs will be assessed, documented, and reported in accordance with ICH GCP guidelines. Section 13.1.1 outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting AEs. Electronic AE case report form (CRF) completion guidelines for investigators as well as training will be provided.

11.5.2 Clinical Laboratory Assessments

Parts A [redacted]

Blood and urine samples will be analyzed at a central laboratory with the exception of urine pregnancy tests, which will be analyzed locally. All blood samples will be collected while subjects are in a seated or supine position. Specific instructions for the collection, processing, and shipment of samples will be provided in a separate Laboratory Manual. Laboratory test results that are abnormal and considered clinically significant must be reported as AEs (see Section 13.1.1.2).

Blood and urine samples for clinical laboratory assessments will be collected according to the schedule of assessments (Table 3-1 [redacted]).

Table 11-2 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 Studies**	
Alanine transaminase	Activated partial thromboplastin time	
Amylase	Prothrombin time	
Lipase	Prothrombin time International	
Gamma-glutamyl transferase	Normalized Ratio	
Protein		
Albumin		
Creatine kinase		
Total cholesterol		
Lactate dehydrogenase		

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

[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.

Clinical laboratory assessments from screening will have no clinically significant findings that preclude participation in the study, as deemed by the investigator, for a subject to receive study drug on Day 1.

Liver function testing (ALT, AST, GGT, ALP, and total bilirubin) must be performed at the scheduled visits and Week 20 (a minimum of every 4 weeks after Week 4). A local laboratory may be used for the Week 20 sample if a subject cannot return to the site for the blood draw; confirmatory testing by the central lab must be performed as soon as possible if liver function tests are determined to be abnormal.

Pregnancy (β-human chorionic gonadotropin) Tests for Females of Childbearing Potential: Any female subject who does not meet the criteria for non-childbearing potential is considered to be of childbearing potential and must have a serum pregnancy test at screening. A definition of non-childbearing potential is provided in Section 11.5.6.1. Serum pregnancy tests will be performed at the study site and analyzed at the central laboratory. Urine pregnancy tests will either be performed and analyzed at the site or, when there is no clinic visit scheduled, at home by using a home kit provided by the site. Results will be reported to the site by telephone. The urine pregnancy test on Day 1 must be negative before the first dose of study drug. Additional pregnancy tests may be required according to local regulations and/or requirements.

CF genotype (Screening Period only): CF genotyping will be performed on all subjects to confirm the genotype documented in the subject's medical record. This assessment does not need to be repeated in the case of rescreening [redacted]

Drug and Alcohol Screening (Screening Period [**Parts A** [redacted] and Day 1 [**Part A Only**]): opiates, methadone, cannabinoids, cocaine, amphetamines/methamphetamines, barbiturates, benzodiazepines, cotinine, and alcohol will be assessed by a urine test. Subjects may undergo random urine drug screen and alcohol testing if deemed appropriate by the investigator. Drug screen result will be negative for all subjects to receive study drug.

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

For the purposes of study conduct and unless noted otherwise, only laboratory tests done in the central laboratory may be used. Local laboratories may be used at the discretion of the local investigator for management of urgent medical issues. If a local laboratory test value is found to be abnormal and clinically significant, it will be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. If it is not possible to send a timely specimen to the central laboratory (e.g., the subject was hospitalized elsewhere), the investigator may base the assessment of an AE on the local laboratory value.

11.5.3 Physical Examinations and Vital Signs

Parts A [redacted]

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

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

Symptom-directed PEs and symptom-directed vital signs assessment may be performed if appropriate.

Weight, height, and BMI (derived) will also be assessed (Section 11.4.4).

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

Arterial oxygen saturation by pulse oximetry will be assessed following at least a 5-minute rest and before study drug dosing. At visits when study drug is taken at the site, pulse oximetry will be collected before study drug dosing.

11.5.4 Electrocardiograms

Parts A [redacted]

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

- The ECG will be done before any other procedures that may affect heart rate, such as blood draws.
- The subject will be instructed to rest for at least 5 minutes before having an ECG.
- ECGs will be performed in triplicate at the Day 1 Visit.

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

To ensure safety of the subjects, a qualified individual at the study site will make comparisons to baseline measurements. If the QTcF is increased by >60 msec from the baseline or an absolute QTcF value is ≥500 msec for any scheduled ECG, 2 additional ECGs will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>60 msec from baseline or ≥500 msec), a single ECG will be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. A subject with a QTcF value above the threshold value will discontinue dosing.

11.5.5 Ophthalmologic Examination

Parts A [redacted]

Ophthalmologic examinations do not need to be completed if there is documentation of bilateral lens removal for the subject.

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

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

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

Any clinically significant abnormal findings will be reported as AEs.

11.5.6 Contraception and Pregnancy

Parts A [redacted]

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

11.5.6.1 Contraception

Parts A [redacted]

Contraception requirement for a couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. True abstinence must be practiced from the Screening Visit through 90 days after the last dose of study drug.
- If the male is infertile (e.g., bilateral orchiectomy). If a male subject is assumed to have complete bilateral absence of the vas deferens, infertility must be documented before the first dose of study drug (e.g., examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound).
- If the female is of non-childbearing potential. To be considered of non-childbearing potential, the female must meet at least 1 of the following criteria:
    - Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females
    - Documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy

  Note: All other females 10 years of age and older (including females with tubal ligations) will be considered to be of childbearing potential.
- Same-sex relationships

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

Table 11-3 Acceptable Methods of Contraception

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

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

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

Additional notes:

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

11.5.6.2 Pregnancy

Parts A[redacted]

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.

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

12 STATISTICAL AND ANALYTICAL PLANS

Parts A [redacted]

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

12.1 Sample Size and Power

Part A

Approximately 12 subjects will be enrolled in Part A. Sample size calculations were determined based on VX-659 PK, using noncompartmental analysis (NCA)-based parameters, such as clearance and volume of distribution. Based on the variability observed in adults, data from 12 subjects will allow 80% power to target a 95% CI within 60% and 140% of the geometric mean estimate of clearance for VX-659.

[redacted]

12.2 Analysis Sets

Parts A [redacted]

Assignment of subjects to analysis sets will be done before the clinical data lock for the study. The analysis set will be defined separately for Part A [redacted]

Safety Set

The Safety Set will include all subjects who received at least 1 dose of study drug. The Safety Set will be used for all safety analyses.

Full Analysis Set (FAS)

The FAS will include all subjects who carry the intended CFTR allele mutation and received at least 1 dose of study drug. The FAS will be used to summarize subject demographics and baseline characteristics, and for analyses of all efficacy endpoints, unless otherwise specified.

All Subjects Set

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

12.3 Statistical Analysis

12.3.1 General Considerations

Parts A [redacted]

Data from Part A [redacted] will be analyzed separately.

Continuous variables will be summarized using the following descriptive summary statistics: number of subjects (n), mean, SD, SE, median, minimum value (min), and maximum value (max). The precision of the measurement for each continuous variable will be specified in the SAP.

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

Treatment-emergent (TE) period for Parts A and B will include the time from the first dose of study drug in the respective Part through 28 days after the last dose, or the completion of study participation date, whichever is earlier.

Baseline for Part A, unless otherwise specified, is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in Part A. For ECGs, baseline will be the average of the 3 pretreatment measurements on Day 1. [redacted]

Absolute change from baseline will be calculated as postbaseline value – baseline value.

Relative change from baseline will be calculated as (postbaseline value – baseline value)/baseline value.

12.3.2 Background Characteristics

Parts A [redacted]

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, study drug exposure, and other background characteristics will be summarized for Part A and [redacted] respectively. All summaries described above will be based on the FAS, unless otherwise specified.

12.3.2.1 Subject Disposition

Parts A [redacted]

The number and percentage of subjects in All Subjects Set and Safety Set will be summarized for Part A; and in All Subjects Set, FAS, and Safety Set will be summarized for [redacted] In addition, the number and percentage of subjects in each disposition category (e.g., completed treatment, completed study; with a breakdown of the reason for study discontinuation or treatment discontinuation) will be summarized.

12.3.2.2 Demographics and Baseline Characteristics

Parts A [redacted]

Demographic, background (e.g., medical history), and baseline characteristics will be summarized separately for Part A [redacted]

The following demographics and baseline characteristics will be summarized: sex, race, ethnicity, age, weight, height, BMI, region, [redacted]

12.3.2.3 Prior and Concomitant Medications

Parts A [redacted]

Medications will be coded using the World Health Organization Drug-Dictionary and categorized as follows for Parts A [redacted]

- **Prior medication:** any medication that administered during the 56 days before the first dose of study drug in the corresponding Part
- **Concomitant medication:** medication continued or newly received during the corresponding TE Period
- **Post-treatment medication:** medication continued or newly received after the corresponding TE Period. [redacted]

A given medication can 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 partial missing start/end date or time and it cannot be determined whether the medication was taken before first dose, concomitantly, or post-treatment, it will be considered as prior, concomitant, and post-treatment.

Prior and post-treatment medications will only be listed and not summarized. The concomitant medications will be summarized descriptively based on the FAS.

12.3.2.4 Study Drug Exposure and Compliance

Parts A [redacted]

Study drug compliance will be measured by the exposure ratio, which is calculated as: 100 × [1 - (Total number of days study drug interruption) / (Duration of study drug exposure in days)]. The total number of days of study drug interrupted is defined as the sum of (number of days of study drug interrupted in each interruption interval); where number of days of study drug interrupted in each interval is defined as the interruption end date - the corresponding interruption start date + 1.

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

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

Duration of treatment and exposure ratio will be summarized using descriptive statistics.

[redacted]

[redacted]

12.3.5 Safety Analysis

Parts A [redacted]

Safety is a secondary objective of Part A, [redacted] All safety analyses will be conducted for Part A [redacted], based on data from the corresponding TE Period in the Safety Set. The overall safety profile of study drug will be assessed based on the following safety and tolerability endpoints:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., hematology, serum chemistry, coagulation, and urinalysis as applicable)
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry
- Ophthalmological examinations

12.3.5.1 Adverse Events

Parts A [redacted]

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

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

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

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

Summaries will be presented by MedDRA System Organ Class and Preferred Term using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once, only the maximum severity level will be presented in the severity summaries, and the strongest relationship level in the relationship summaries. An AE overview table will be provided. In addition, a listing containing individual subject level AE data for all deaths and other serious and significant AEs

will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

12.3.5.2 Clinical Laboratory Assessments

Parts A [redacted]

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

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

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

12.3.5.3 Electrocardiogram

Parts A [redacted]

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

The number and percentage of subjects meeting a threshold analysis criterion during the TE Period will be summarized. The threshold analysis criteria will be provided in the SAP.

12.3.5.4 Vital Signs

Parts A [redacted]

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

The number and percentage of subjects meeting a threshold analysis criterion during the TE Period will be summarized. The threshold analysis criteria will be provided in the SAP.

12.3.5.5 Pulse Oximetry

Parts A [redacted]

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

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

12.3.5.6 Ophthalmologic Examinations

Parts A [redacted]

The ophthalmologic examination results will be presented in individual subject data listings.

12.3.5.7 Physical Examination

Parts A [redacted]

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

[redacted]

12.4 Clinical Pharmacology Analysis

12.4.1 Pharmacokinetic Analysis

Parts A [redacted]

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

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

12.4.2 Pharmacokinetic/Pharmacodynamic Analyses

Parts A [redacted]

PK/PD analyses may be performed on selected PD assessments, which include [redacted], as well as other endpoints such as BMI, BMI z-score, or [redacted]

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

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

All subsections below apply to Parts A [redacted]

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

Study assessments including laboratory tests, ECGs, PEs, and vital signs will be assessed and those deemed to have clinically-significant worsening from baseline will be documented as an AE. When possible, a clinical diagnosis for the study assessment will be provided, rather than the abnormal test result alone (e.g., urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself will be listed as the AE (e.g., bacteria in urine or decreased hemoglobin).

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

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

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

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

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time the ICF is signed until the subject completes study participation, as defined in Section 9.1.6.

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

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

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed 28 September 2017). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." In considering the severity of an AE in a pediatric subject, the investigator will consider that reference ranges for pediatric clinical laboratory parameters may differ from those given in the CTCAE. The severity of an AE that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

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

13.1.1.5 Adverse Event Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug(s). Causality will be classified using the categories presented in Table 13-2.

Table 13-2 Classifications for AE Causality

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

13.1.1.6 Study Drug Action Taken

The investigator will classify the study drug action taken with regard to the AE. The action taken will be classified according to the categories shown in Table 13-3.

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

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

13.1.1.7 Adverse Event Outcome

An AE will be followed until the investigator has determined and provided the final outcome. The outcome will be classified according to the categories shown in Table 13-4.

Table 13-4 Classifications for Outcome of an AE

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

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

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

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

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the subject signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure will not be considered to indicate an SAE, unless an AE caused the hospitalization or procedure to be rescheduled sooner or to be prolonged relative to what was planned. In addition, hospitalizations clearly not associated with an AE (e.g., social hospitalization for purposes of respite care) will not be considered to indicate an SAE.

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

13.1.2.2 Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent through completion of study participation, regardless of causality, will be reported by the investigator to Vertex GPS. In addition, all SAEs that occur after completion of study participation and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours**.

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

13.1.2.3 Reporting Serious Adverse Events

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

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

For questions, contact telephone: [redacted]

13.1.2.4 Expedited Reporting and Investigator Safety Letters

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

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

13.2 Administrative Requirements

13.2.1 Ethical Considerations

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

13.2.2 Subject Information and Informed Consent and Assent

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

13.2.3 Investigator Compliance

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

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

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

For sites participating in the study in the US, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated regulations, an executed HIPAA authorization shall be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization shall comply with all HIPAA requirements including authorization allowing the site access to and use of the subject's personally identifiable health information, authorization for the site to disclose such information to Vertex, the FDA, and other parties requiring access under the protocol, and statements as to the purpose for which such information may be used and for how long.

13.2.6 Record Retention

The investigator will maintain all study records according to ICH GCP guidelines and/or applicable local regulatory requirement(s), whichever is longest, as described in the Clinical Trial Agreement. If the investigator withdraws from the responsibility of keeping the study records, custody will be transferred to a person willing to accept the responsibility and Vertex will be notified.

13.2.7 Study Termination

At any time, Vertex may terminate this study in its entirety or may terminate this study at any particular site. In addition, for reasonable cause, either the investigators or their IRBs/IECs may terminate the study at their center.

Conditions that may lead to reasonable cause and warrant termination include, but are not limited to:

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the FDA or other regulatory authority

Written notification that includes the reason for the clinical study termination is required.

13.2.8 End of Study

The end of study is defined as the last scheduled visit or, for subjects who have been lost to follow-up, the last contact, whichever occurs later, for the latest completing subject in the study.

13.3 Data Quality Assurance

Vertex or its designated representative will conduct a study site visit to verify the qualifications of each investigator, inspect clinical study site facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure, validated, web-based electronic data capture (EDC) application. Vertex will have read-only access to site-entered clinical data in the EDC application.

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

13.4 Monitoring

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

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

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

13.5 Electronic Data Capture

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

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

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

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

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

13.6 Publications and Clinical Study Report

13.6.2 Clinical Study Report

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

14 REFERENCE

1 Cystic Fibrosis Foundation. What is cystic fibrosis? Available at: https://www.cff.org/What-is-CF/About-Cystic-Fibrosis/. Accessed 03 September 2015.

2 Kreindler JL. Cystic fibrosis: Exploiting its genetic basis in the hunt for new therapies. Pharmacol Ther. 2010;125(2):219-29.

3 Stern M, Wiedemann B, Wenzlaff P. From registry to quality management: the German Cystic Fibrosis Quality Assessment project 1995 - 2006. Eur Respir J. 2008;31(1):29-35.

4 Cystic Fibrosis Trust. UK Cystic Fibrosis Trust Annual Review 2010. Bromley, Kent, UK: Cystic Fibrosis Trust; 2012.

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6 Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.

7 Counahan R, Chantler C, Ghazali S, Kirkwood B, Rose F, Barratt TM. Estimation of glomerular filtration rate from plasma creatinine concentration in children. Arch Dis Child. 1976;51(11):875-78.

8 Konstan M, McKone EF, Moss RB, Marigowda G, Cooke J, Huang X, et al. Evidence for reduced rate of lung function decline and sustained benefit with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation. Lancet Haematol. 2016;

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13 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.

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APPENDIX A Eligible MF *CFTR* Mutations

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

(1) biological plausibility of no translated protein (genetic sequence predicts the complete absence of CFTR protein), or

(2) in vitro testing that supports lack of responsiveness to TEZ, IVA, or TEZ/IVA, and evidence of clinical severity on a population basis (as reported in large patient registries).

Inclusion of MF Mutations Based on In Vitro Testing

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

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

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

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

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

Eligible MF Mutations

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

Non-exhaustive List of Minimal Function *CFTR* Mutations Eligible for VX17-659-106

MF Mutation Category	Mutation				
Nonsense mutations	Q2X	L218X	Q525X	R792X	E1104X
	S4X	Q220X	G542X	E822X	W1145X
	W19X	Y275X	G550X	W882X	R1158X
	G27X	C276X	Q552X	W846X	R1162X
	Q39X	Q290X	R553X	Y849X	S1196X
	W57X	G330X	E585X	R851X	W1204X
	E60X	W401X	G673X	Q890X	L1254X
	R75X	Q414X	Q685X	S912X	S1255X
	L88X	S434X	R709X	Y913X	W1282X
	E92X	S466X	K710X	Q1042X	Q1313X
	Q98X	S489X	Q715X	W1089X	Q1330X
	Y122X	Q493X	L732X	Y1092X	E1371X
	E193X	W496X	R764X	W1098X	Q1382X
	W216X	C524X	R785X	R1102X	Q1411X
Canonical splice mutations	185+1G→T	711+5G→A	1717-8G→A	2622+1G→A	3121-1G→A
	296+1G→A	712-1G→T	1717-1G→A	2790-1G→C	3500-2A→G
	296+1G→T	1248+1G→A	1811+1G→C	3040G→C	3600+2insT
	405+1G→A	1249-1G→A	1811+1.6kbA→G	(G970R)	3850-1G→A
	405+3A→C	1341+1G→A	1811+1643G→T	3120G→A	4005+1G→A
	406-1G→A	1525-2A→G	1812-1G→A	3120+1G→A	4374+1G→T
	621+1G→T	1525-1G→A	1898+1G→A	3121-2A→G	
	711+1G→T		1898+1G→C		
Small (≤3 nucleotide) insertion/deletion (ins/del) frameshift mutations	182delT	1078delT	1677delTA	2711delT	3737delA
	306insA	1119delA	1782delA	2732insA	3791delC
	306delTAGA	1138insG	1824delA	2869insG	3821delT
	365-366insT	1154insTC	1833delT	2896insAG	3876delA
	394delTT	1161delC	2043delG	2942insT	3878delG
	442delA	1213delT	2143delT	2957delT	3905insT
	444delA	1259insA	2183AA→G [a]	3007delG	4016insT
	457TAT→G	1288insTA	2184delA	3028delA	4021dupT
	541delC	1343delG	2184insA	3171delC	4022insT
	574delA	1471delA	2307insA	3171insC	4040delA
	663delT	1497delGG	2347delG	3271delGG	4279insA
	849delG	1548delG	2585delT	3349insT	4326delTC
	935delA	1609del CA	2594delGT	3659delC	
Non-small (>3 nucleotide) insertion/deletion (ins/del) frameshift mutations	CFTRdele1	CFTRdele16-17b	1461ins4		
	CFTRdele2	CFTRdele17a,17b	1924del7		
	CFTRdele2,3	CFTRdele17a-18	2055del9→A		
	CFTRdele2-4	CFTRdele19	2105-2117del13insAGAAA		
	CFTRdele3-10,14b-16	CFTRdele19-21	2372del8		
	CFTRdele4-7	CFTRdele21	2721del11		
	CFTRdele4-11	CFTRdele22-24	2991del32		
	CFTR50kbdel	CFTRdele22,23	3121-977_3499+248del2515		
	CFTRdup6b-10	124del23bp	3667ins4		
	CFTRdele11	602del14	4010del4		
	CFTRdele13,14a	852del22	4209TGTT→AA		
	CFTRdele14b-17b	991del5			

Non-exhaustive List of Minimal Function *CFTR* Mutations Eligible for VX17-659-106

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

CFTR: cystic fibrosis transmembrane conductance regulator; IVA: ivacaftor; SwCl: sweat chloride; TEZ: tezacaftor

Source: CFTR2.org [Internet]. Baltimore (MD): Clinical and functional translation of CFTR. The Clinical and Functional Translation of CFTR (CFTR2), US Cystic Fibrosis Foundation, Johns Hopkins University, the Hospital for Sick Children. Available at: http://www.cftr2.org/. Accessed 15 February 2016.

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

[a] Also known as 2183delAA→G.

[b] Unpublished data.

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX18-659-106	Version #: 1.0	Version Date: 14 May 2018
Study Title: A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-659/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age		

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

[redacted]

15.2 Investigator Signature Page

Protocol #: VX18-659-106	Version #: 1.0	Version Date: 14 May 2018
Study Title: A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-659/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age		

I have read Protocol VX18-659-106, Version 1.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-659, tezacaftor, and ivacaftor and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date