1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Elexacaftor/Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 Through 5 Years of Age

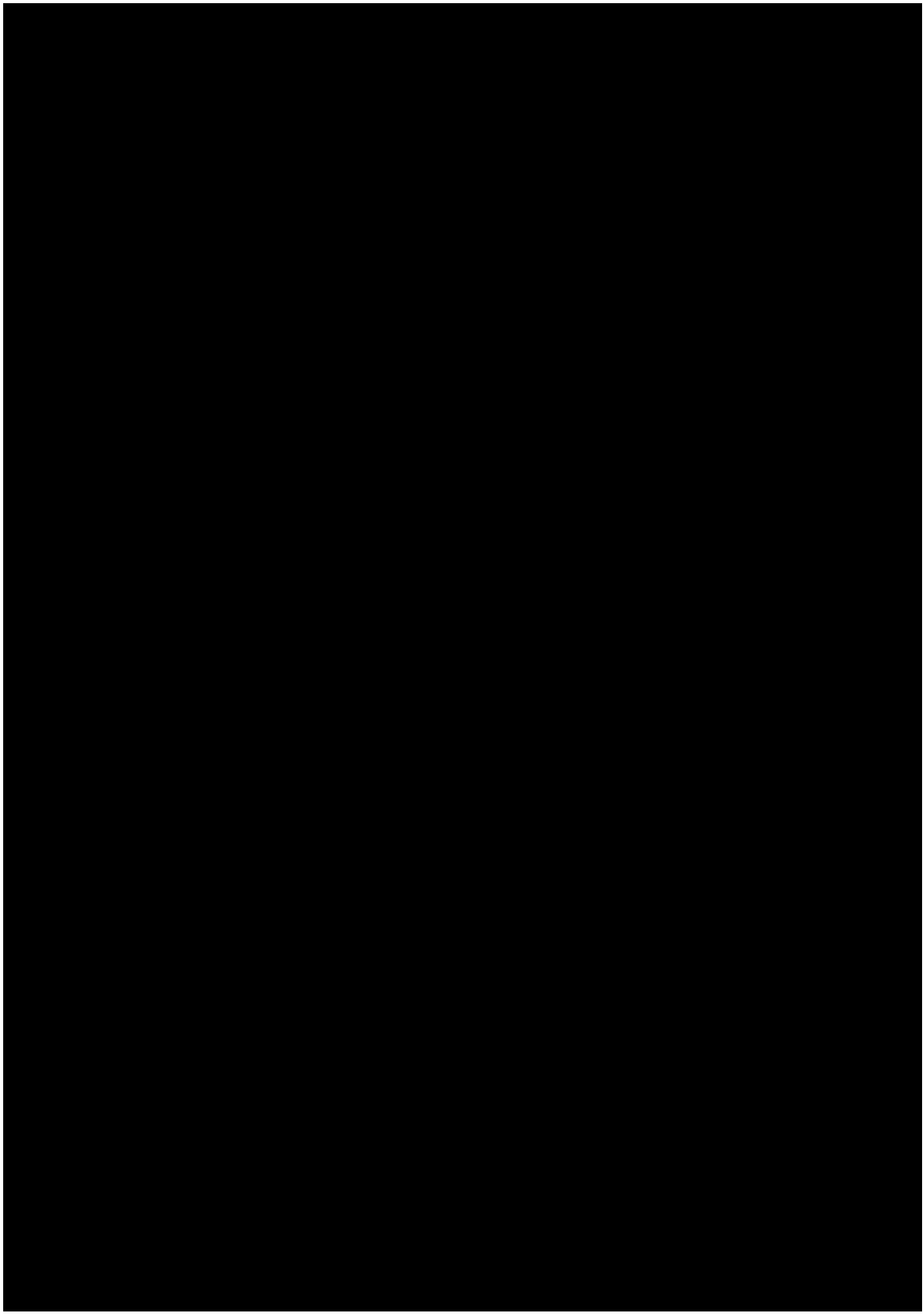
Vertex Study Number: VX20-445-111

[redacted]

EudraCT Number: 2020-002251-38

Date of Protocol: 21 October 2021 (Version 3.0)

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



2 PROTOCOL SYNOPSIS

Title A Phase 3 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Elexacaftor/Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 Through 5 Years of Age

Brief Title Evaluation of ELX/TEZ/IVA in Cystic Fibrosis (CF) Subjects 2 Through 5 Years

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

Objectives

Part A

Primary Objectives

- To evaluate the PK of elexacaftor (ELX), tezacaftor (TEZ), and ivacaftor (IVA) when dosed in triple combination (TC)
- To evaluate the safety and tolerability of ELX/TEZ/IVA

Part B

Primary Objective

To evaluate the safety and tolerability of ELX/TEZ/IVA

Secondary Objectives

- To evaluate the PK of ELX, TEZ, and IVA
- To evaluate the pharmacodynamics (PD) of ELX/TEZ/IVA
- To evaluate the efficacy of ELX/TEZ/IVA

Endpoints

Part A

Primary Endpoints

- PK parameters of ELX, TEZ, IVA, and relevant metabolites
- Safety and tolerability assessments as determined by adverse events (AEs), clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry

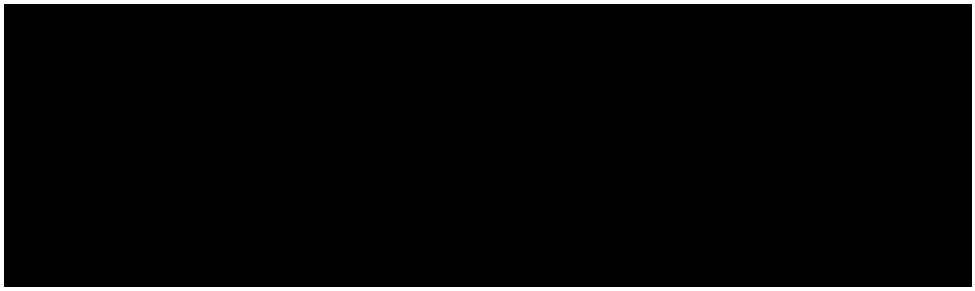
Part B

Primary Endpoint

Safety and tolerability assessments as determined by AEs, clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry

Secondary Endpoints

- PK parameters of ELX, TEZ, IVA, and relevant metabolites
- Absolute change in sweat chloride (SwCl) from baseline through Week 24
- Absolute change in lung clearance index $(LCI)_{2.5}$ from baseline through Week 24



[redacted]

Number of Subjects

Part A

Approximately 14 subjects with F/F or F/MF genotypes are planned for enrollment. Subjects who participate in Part A may participate in Part B.

Part B

Approximately 70 subjects are planned for enrollment. At least 30 subjects with F/MF genotypes and at least 15 subjects with F/F genotypes are targeted for enrollment. At least 25 subjects should be between 2 and 3 years of age (inclusive).

Study Population

Part A

Male and female CF subjects 2 through 5 years of age (inclusive) with F/MF or F/F genotypes. Subjects must weigh ≥14 kg at Day 1.

Part B

Male and female CF subjects 2 through 5 years of age (inclusive) who have at least 1 *F508del* mutation in the *CFTR* gene or an ELX/TEZ/IVA-responsive *CFTR* mutation. Subjects must weigh ≥10 kg at the Screening Visit.

Investigational Drug

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

Activity: CFTR correctors (ELX and TEZ) and potentiator (IVA)

Strength and route of administration:

- **Parts A and B:** 100 mg ELX/50 mg TEZ/75 mg IVA FDC granules for oral administration **AND** 75 mg IVA granules for oral administration
- **Part B Only:** 80 mg ELX/40 mg TEZ/60 mg IVA FDC granules for oral administration **AND** 59.5 mg IVA granules for oral administration

Study Duration

Part A

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

Part B

Excluding the Screening Period, subjects will participate in the study for up to 28 weeks (± 7 days)

Study Design

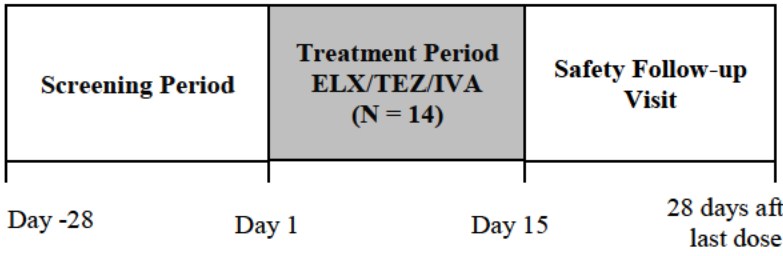
This is a Phase 3, 2-part (Parts A and B), multicenter study evaluating the safety, tolerability, PK, PD, and efficacy of ELX/TEZ/IVA in CF subjects 2 through 5 years of age (inclusive).

Part A

A schematic of the study design for Part A is provided below. Approximately 14 subjects (F/F or F/MF genotypes) will be enrolled. During the Treatment Period, subjects will be administered ELX/TEZ/IVA for approximately 15 days. Safety, tolerability, and available PK data from Part A will be reviewed by Vertex

to confirm or adjust the dose(s) chosen for Part B. Additional subjects may be enrolled as needed in Part A, based on emerging PK data, in order to provide sufficient information to select the dose(s) for Part B.

Figure 2-1 VX20-445-111 Part A Study Design



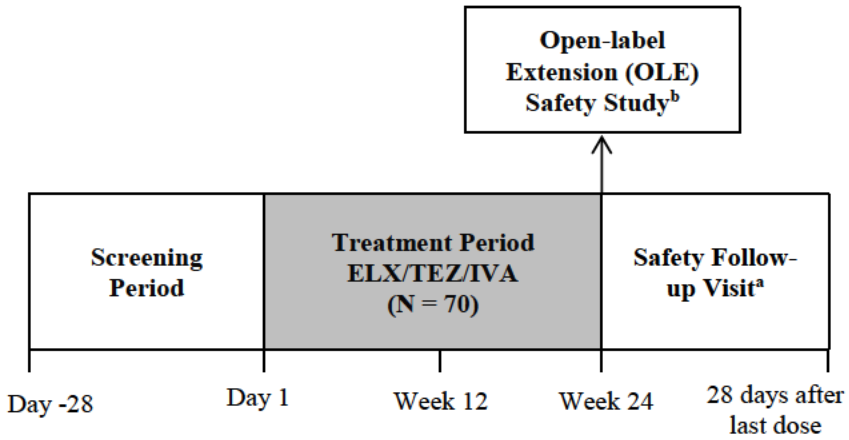
ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor
Note: ELX/TEZ/IVA will be administered from Day 1 through Day 15. On Day 15, only the morning dose will be administered.

Part B

A schematic of the study design for Part B is provided below. Part B will initiate after available data from Part A has been reviewed by Vertex and the Part B dose(s) has been confirmed or adjusted. Part B will enroll approximately 70 subjects, of which at least 30 subjects will have F/MF genotypes and at least 15 subjects will have the F/F genotype. At least 25 subjects should be between 2 and 3 years of age (inclusive). During the Treatment Period, subjects will be administered ELX/TEZ/IVA for approximately 24 weeks.

Subjects who are eligible will be offered the opportunity to enroll in an open-label extension (OLE) safety study.

Figure 2-2 VX20-445-111 Part B Study Design



ELX: elexacaftor; IVA: ivacaftor; OLE: open-label extension; TEZ: tezacaftor

[a] The Safety Follow-up Visit is not required for subjects who enroll in an OLE safety study within 28 days of the last scheduled visit in the Treatment Period.

[b] Subjects who are eligible will be offered the opportunity to enroll in an OLE safety study evaluating ELX/TEZ/IVA.

Table 2-1 Parts A and B Doses

Subject Weight at Day 1	ELX Dose	TEZ Dose	IVA Dose
Part A			
≥14 kg only	100 mg qd	50 mg qd	75 mg q12h
Part B			
≥14 kg	100 mg qd	50 mg qd	75 mg q12h
≥10 kg to <14 kg	80 mg qd	40 mg qd	60 mg qAM 59.5 mg qPM

ELX: elexacaftor; IVA: ivacaftor; qAM: once every morning; qd: once daily; q12h: every 12 hours; qPM: once every evening; TEZ: tezacaftor

Assessments

Parts A and B

PK Assessments:

PK parameters of ELX, TEZ, IVA, and relevant metabolites

Safety Assessments:

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

Part B

PD Assessment:

SwCl

Efficacy Assessments:

Multiple-breath washout (MBW; subjects ≥3 years of age at screening of Part B),

[redacted]

Statistical Analyses

Data from Part A and Part B will be analyzed separately.

Part A

Approximately 14 subjects will be enrolled in Part A. Sample size calculations were determined based on ELX and M23-445 estimates of clearance. Assuming that the variability in this age group is the same as the variability observed in adults, data from 14 subjects will allow at least 80% power to target a 95% CI within 60% and 140% of the geometric mean estimate of clearance for ELX and M23-445.

Part B

Approximately 70 subjects will be enrolled. With 56 subjects expected to complete Part B, there is a >90% chance of observing an AE in at least 1 subject if the true incidence rate is 5%, and a >95% chance of observing an AE in at least 1 subject if the true incidence rate is 10%.

For the primary endpoint, summary statistics will be provided for treatment-emergent AEs, clinical laboratory assessments, standard 12-lead ECGs, vital signs, and pulse oximetry.

DMC Reviews An external data monitoring committee (DMC) will conduct periodic safety review(s) of study data as outlined in the DMC charter.

3 SCHEDULE OF ASSESSMENTS

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), Table 3-3 (Part B Screening Period), and Table 3-4 (Part B Treatment Period and Safety Follow-up Visit).

Table 3-1 Study VX20-445-111, Part A Screening Period

Event/Assessment	Screening Visit Day -28 to Day -1	Comments
Informed consent (and assent)	X	
Demographics	X	Section 11.1
Medical history	X	Section 11.1
Ophthalmologic examination	X	Conducted by an ophthalmologist or optometrist (Section 11.5.5)
Full physical examination	X	Section 11.5.3
Weight [redacted]	X	Measured with shoes off (Section 11.4.3)
Vital signs and pulse oximetry	X	Performed after the subject has been at rest for at least 5 minutes (Section 11.5.3)
Standard 12-lead ECG	X	Performed before any other procedures that may affect heart rate (HR), such as blood draws, and in the supine position after the subject has been at rest for at least 5 minutes (Section 11.5.4)
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 chemistry	X	Section 11.5.2
Hematology	X	
Coagulation	X	
Urinalysis	X	
Medications review	X	Information regarding medications taken within 56 days before the Screening Visit will be collected (Section 9.5)
Adverse events	**Continuous, From Signing of ICF through Completion of Study Participation**	Section 13.1; completion of study participation is defined in Section 9.1.6.

AE: adverse event; *CFTR*: cystic fibrosis transmembrane conductance regulator gene; ECG: electrocardiogram; HR: heart rate; ICF: informed consent form; SAE: serious adverse event

Table 3-2 Study VX20-445-111, Part A Treatment Period and Safety Follow-up Visit

Assessment[a]	Day 1	Day 2 and Day 4 (± 1 Day)	Day 8 (± 1 Day)	Day 15 (± 1 Day)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)	Comments
Clinic visit	X		X	X	X	X	See Section 9.1.8 for use of remote measures in extenuating circumstances.
Telephone contact		X					Assess the subject's status, any AEs, concomitant medications, treatments, and procedures.
Safety Assessments							
Full physical examination	X			X	X	X	Symptom-directed physical examinations will occur at any time during the study if deemed necessary by the investigator (Section 11.5.3).
Weight [redacted]	X			X	X	X	Measured with shoes off (Section 11.4.3).
Vital signs and pulse oximetry	X		X	X	X	X	Performed after the subject has been at rest for at least 5 minutes (Section 11.5.3).
Standard 12-lead ECG	X		X	X	X	X	**Days 1 and 8:** before the AM dose **Day 15:** before the AM dose and 4 hours (± 30 min) after the AM dose Performed before any other procedures that may affect heart rate (HR), such as blood draws, and in the supine position after the subject has been at rest for at least 5 minutes (Section 11.5.4).
Serum chemistry	X		X	X	X	X	Section 11.5.2
Hematology	X		X	X	X	X	
Coagulation	X			X			
Observation 4 hours after the AM dose	X						Section 9.6.1
Medications review	**Continuous, From Signing of ICF Through Completion of Study Participation**						Completion of study participation is defined in Section 9.1.6.
Treatments and procedures review							
Adverse events	**Continuous, From Signing of ICF Through Completion of Study Participation**						Section 13.1; completion of study participation is defined in Section 9.1.6.

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

Table 3-2 Study VX20-445-111, Part A Treatment Period and Safety Follow-up Visit

Assessment[a]	Day 1	Day 2 and Day 4 (± 1 Day)	Day 8 (± 1 Day)	Day 15 (± 1 Day)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)	Comments
PK Assessments							
PK sampling	X		X	X			**Day 1:** before the AM dose, and at 2 hours after the AM dose **Day 8**: before the AM dose, and at 1.5 hours after the AM dose **Day 15:** before the AM dose, and at 3.5 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							
Study drug dosing	**ELX/TEZ/IVA (Day 1 through Day 15; AM 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.
Study drug count			X	X	X		Section 10.4

AE: adverse event; AM: morning; ECG: electrocardiogram; ELX: elexacaftor; ETT: early termination of treatment; HR: heart rate; ICF: informed consent form; IVA: ivacaftor; PK: pharmacokinetic; SAE: serious adverse event; TEZ: tezacaftor

Table 3-3 Study VX20-445-111, Part B Screening Period

Event/Assessment	Screening Visit Day -28 to Day -1	Comments
Informed consent (and assent)	X	
Demographics	X	Section 11.1
Medical history	X	Section 11.1
Ophthalmologic examination	X	Conducted by an ophthalmologist or optometrist (Section 11.5.5)
Full physical examination	X	Section 11.5.3
Weight [redacted]	X	Measured with shoes off (Section 11.4.3)
Vital signs and pulse oximetry	X	Performed after the subject has been at rest for at least 5 minutes (Section 11.5.3)
Standard 12-lead ECG	X	Performed before any other procedures that may affect heart rate (HR), such as blood draws, and in the supine position after the subject has been at rest for at least 5 minutes (Section 11.5.4)
Multiple-breath washout	X	Performed in multiple replicates pre- or post-bronchodilator in subjects ≥3 years of age at screening (Section 11.4.2).
Sweat chloride	X	Section 11.4.1
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). This assessment does not need to be repeated for confirmed subjects in Part A who wish to participate in Part B. Subjects who have been enrolled whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9). If a subject weighs <11 kg at the Screening Visit and requires an additional blood sample for a deletion/duplication assay, this second tube should be drawn at the Day 1 Visit.
[redacted]		
Serum chemistry	X	Must be obtained from a blood draw taken up to 9 days before Day 1 dosing. The results must be received and reviewed before the first dose of study drug (Section 11.5.2).
Hematology	X	A single set of pre-dose hematology and coagulation assessments will be obtained from a blood draw taken up to 9 days before Day 1 dosing. The results must be received and reviewed before the first dose of study drug (Section 11.5.2).
Coagulation	X	
Urinalysis	X	Section 11.5.2
Medications review	X	Information regarding medications taken within 56 days before the Screening Visit will be collected (Section 9.5)
Adverse events	**Continuous, From Signing of ICF through Completion of Study Participation**	Section 13.1; completion of study participation is defined in Section 9.1.6.

AE: adverse event; CFTR: cystic fibrosis transmembrane conductance regulator gene; ECG: electrocardiogram; HR: heart rate; ICF: informed consent form; SAE: serious adverse event

Table 3-4 Study VX20-445-111, Part B Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug[b])	Comments
Clinic visit	X		X	X	X	X	X		X	X	X	See Section 9.1.8 for use of remote measures in extenuating circumstances.
Telephone contact		X						X				Assess the subject's status, any AEs, concomitant medications, treatments, and procedures.
Safety and Efficacy Assessments												
Ophthalmologic examination									X at or up to 4 weeks before	X		Section 11.5.5
Full physical examination	X					X			X	X		Symptom-directed physical examinations will occur at any time during the study if deemed necessary by the investigator (Section 11.5.3).
Weight [redacted]	X		[redacted]									Measured with shoes off (Section 11.4.3).

[a] All assessments will be performed before study drug dosing unless noted otherwise. For any assessments with multiple time points for an individual visit, only 1 set of assessments will be collected if study drug is not administered on the day of the visit (i.e., study drug interruption or permanent discontinuation of study drug).

[b] The Safety Follow-up Visit is not required for subjects who complete the Week 24 Visit and enroll in the open-label extension (OLE) safety study within 28 days after the last dose.

Table 3-4 Study VX20-445-111, Part B Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug[b])	Comments
Vital signs and pulse oximetry	X		X	X	X	X	X		X	X	X	Performed after the subject has been at rest for at least 5 minutes (Section 11.5.3)
Standard 12-lead ECG	X		X			X			X	X	X	Performed before any other procedures that may affect heart rate (HR), such as blood draws, and in the supine position after the subject has been at rest for at least 5 minutes (Section 11.5.4).
Sweat chloride	X			X		X			X	X		Section 11.4.1
Multiple-breath washout	X			X		X			X	X		Performed in multiple replicates pre-bronchodilator in subjects ≥3 years of age at screening (Section 11.4.2).

Table 3-4 Study VX20-445-111, Part B Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug[b])	Comments
Serum chemistry	X		X	X	X	X	X	X	X	X	X	Serum chemistry will be drawn prior to study drug dosing on Day 1. Liver function testing (ALT, AST, GGT, ALP, and total bilirubin) must be performed at the scheduled visits and at 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 study site for the blood draw (Section 11.5.2).
Hematology			X	X[c]	X	X	X		X	X	X	Section 11.5.2
Coagulation									X	X	X	
Urinalysis	X								X	X		

[c] It is recommended that subjects weighing <10.4 kg do not complete the Week 4 hematology blood draw.

Table 3-4 Study VX20-445-111, Part B Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug[b])	Comments
Observation 4 hours after the AM dose	X											Section 9.6.1
[redacted]												
Medications review	**Continuous, From Signing of ICF Through Completion of Study Participation**											Completion of study participation is defined in Section 9.1.6.
Treatments and procedures review												
Adverse events	**Continuous, From Signing of ICF Through Completion of Study Participation**											Section 13.1; completion of study participation is defined in Section 9.1.6.

Table 3-4 Study VX20-445-111, Part B Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug[b])	Comments
[redacted]												

Table 3-4 Study VX20-445-111, Part B Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug[b])	Comments
PK Assessments												
PK sampling			X	X		X	X			X		**Day 15, Week 12, and Week 16:** before the AM dose **Week 4**: before the AM dose, and at 2.5 and 5.5 hours after the AM dose. See Table 11-1 for details.
Study Drug Administration												
Study drug dosing	**ELX/TEZ/IVA (Day 1 through evening before Week 24 Visit)**											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.
[redacted]												
Study drug count			X	X	X	X	X		X	X		Section 10.4

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; ECG: electrocardiogram; ELX: elexacaftor; ETT: early termination of treatment; GGT: gamma-glutamyl transferase; HR: heart rate; ICF: informed consent form; IRT: immunoreactive trypsinogen; IVA: ivacaftor; PEx: pulmonary exacerbation; PK: pharmacokinetic; SAE: serious adverse event; TEZ: tezacaftor

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List of Abbreviations

Abbreviation	Definition
ADL	activities of daily living
AEs	adverse events
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
[redacted]	[redacted]
CD	compact disc
CF	Cystic Fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator gene
CI	confidence interval
CPAP	clinical pharmacology analysis plan
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
ELX	elexacaftor
ETT	Early Termination of Treatment
EU	European Union
F508del	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
[redacted]	[redacted]
FEV_1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GPS	Global Patient Safety
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
IND	Investigational New Drug (application) (US)
IRB	institutional review board

Abbreviation	Definition
[redacted]	[redacted]
IV	intravenous
IVA	ivacaftor
IWRS	interactive web response system
LCI	lung clearance index
$LCI_{2.5}$	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value
LUM	lumacaftor
max	maximum value
MBW	Multiple-breath washout
MF	minimal function
min	minimum value
MMRM	mixed-effects model for repeated measures
N	total sample size
P	probability
PC	publication committee
PD	Pharmacodynamic(s)
PEs	physical examinations
PEx	pulmonary exacerbations
P-gp	P-glycoprotein
PIs	principal investigators
PK	Pharmacokinetic(s)
PR	PR interval, segment
q12h	every 12 hours
qAM	once every morning
qd	once daily
qPM	once every evening
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 Fredericia's formula
RR	interval from the onset of 1 QRS complex to the next; use R-R if using with "intervals", i.e., "R-R interval"
SAE	serious adverse event
SAP	statistical analysis plan
SC	steering committee
SD	standard deviation
SI	SI units (International System of Units)
SUSARs	suspected, unexpected, serious adverse reaction
SwCl	sweat chloride
TC	triple combination
TE	Treatment-emergent

Abbreviation	Definition
TEAEs	Treatment-emergent adverse events
TEZ	tezacaftor
ULN	upper limit of normal
US	United States
USA	United States of America

5 INTRODUCTION

5.1 Background

Cystic fibrosis (CF) is an autosomal recessive genetic disease with serious morbidities and frequent premature mortality. CF affects more than 70,000 individuals worldwide[1] (approximately 31,000 in the US[2] and 48,000 in the EU[3]).

CF is caused by decreased quantity and/or function of the CFTR protein due to mutations in the *CFTR* gene.[4] CFTR is a channel that regulates the flow of chloride and other anions across epithelia in multiple organs and tissues, including the lungs, pancreas and other gastrointestinal organs, and sweat glands.[5] Despite progress in the treatment of CF with antibiotics and mucolytics, the current median age at death among people with CF is approximately 30 years, and the predicted median age of survival is approximately 47 years.[2, 3] More effective treatments are needed for CF.

The most common disease-causing mutation is *F508del*: approximately 84.7% of people with CF in the US and 81.1% in Europe have at least one *F508del* allele.[2, 3]

At present CF does not have a cure. CFTR modulators (i.e., correctors and potentiators) represent a major advancement in the treatment of CF because they are systemic therapies that target the underlying cause of the disease and have been shown to improve CF survival by modifying the course of disease.[6, 7] The clinical testing and regulatory approval of CFTR modulators in certain countries for the treatment of people with CF caused by specific *CFTR* genotypes has established the therapeutic value of specific regimens developed by Vertex. These treatment regimens include ivacaftor (IVA) monotherapy (Kalydeco™), lumacaftor (LUM)/IVA dual combination therapy (Orkambi™), tezacaftor (TEZ)/IVA dual combination therapy (Symdeko™, Symkevi™) and elexacaftor (ELX)/TEZ/IVA triple combination (TC) therapy.

The ELX/TEZ/IVA regimen is the first medicine to demonstrate clinical benefit in patients with a single *F508del* allele, regardless of the mutation of the second allele. A pivotal Phase 3 program in CF subjects 12 years of age or older demonstrated that ELX/TEZ/IVA provides substantial improvements in lung function, CFTR function, and nutritional status, and was generally safe and well tolerated with a low rate of treatment discontinuation.

5.2 Study Rationale

Given the progressive nature of CF, there is a strong rationale for preventing disease progression by treating patients earlier in life. Vertex evaluated ELX/TEZ/IVA TC therapy in Phase 3 studies in adult and adolescent CF subjects with 1 or 2 copies of the *F508del* mutation, namely those with F/MF and F/F genotypes. Given the clinical benefit seen in a Phase 3 study of adults with CF with ELX/TEZ/IVA, the present study is designed to obtain pharmacokinetic (PK), safety, tolerability, and pharmacodynamic (PD) information to expand the evaluation of ELX/TEZ/IVA in the pediatric population 2 through 5 years of age (inclusive) with F/MF or F/F genotypes (Part A) or who have at least 1 *F508del* mutation in the *CFTR* gene or an ELX/TEZ/IVA-responsive *CFTR* mutation (Part B).

6 STUDY OBJECTIVES

6.1 Primary Objectives

Part A

- To evaluate the PK of ELX, TEZ, and IVA when dosed in TC
- To evaluate the safety and tolerability of ELX/TEZ/IVA

Part B

To evaluate the safety and tolerability of ELX/TEZ/IVA

6.2 Secondary Objectives

Part A

None

Part B

- To evaluate the PK of ELX, TEZ, and IVA
- To evaluate the PD of ELX/TEZ/IVA
- To evaluate the efficacy of ELX/TEZ/IVA

7 STUDY ENDPOINTS

7.1 Primary Endpoints

Part A

- PK parameters of ELX, TEZ, IVA, and relevant metabolites
- Safety and tolerability assessments as determined by adverse events (AEs), clinical laboratory values, standard 12-lead electrocardiograms (ECGs), vital signs, and pulse oximetry

Part B

Safety and tolerability assessments as determined by AEs, clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry

7.2 Secondary Endpoints

Part A

None

Part B

- PK parameters of ELX, TEZ, IVA, and relevant metabolites
- Absolute change in sweat chloride (SwCl) from baseline through Week 24
- Absolute change in lung clearance index $(LCI)_{2.5}$ from baseline through Week 24

[redacted]

8 STUDY POPULATION

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

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

8.1 Inclusion Criteria

1. Subject's legally appointed and authorized representative will sign and date an informed consent form (ICF).
2. Subjects (males and females), 2 through 5 years of age, inclusive, on the date of informed consent (and assent, as applicable).
3. In **Part A**, subjects must weigh ≥14 kg at Day 1. In **Part B**, subjects must weigh ≥10 kg at the Screening Visit.
4. Confirmed diagnosis of CF as determined by the investigator.
5. In **Part A,** subjects who are homozygous for *F508del* (F/F genotype) or heterozygous for *F508del* and an MF mutation that is not responsive to IVA and TEZ/IVA (F/MF genotypes; Appendix A). In **Part B,** subjects who have at least 1 *F508del* mutation in the *CFTR* gene or an ELX/TEZ/IVA-responsive *CFTR* mutation (Appendix B).

    - Genotype should be confirmed at the Screening Visit. This assessment does not need to be repeated for confirmed subjects in Part A who wish to participate in Part B.
    - 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 stable CF disease at the start of the Treatment Period as deemed by the investigator.
7. Subjects who are willing to remain on a stable CF medication regimen (other than *CFTR* modulators) through Day 15 (**Part A**) or through Week 24 (**Part B**) or, if applicable, through the Safety Follow-up Visit.
8. As judged by the investigator, the parent or legal guardian must be able to understand protocol requirements, restrictions, and instructions and the parent or legal guardian should be able to ensure that the subject will comply with and is likely to complete the study as planned.

8.2 Exclusion Criteria

1. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This includes, but is not limited to, the following:
   - Clinically significant cirrhosis with or without portal hypertension
   - Solid organ or hematological transplantation
   - Cancer
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, aspartate transaminase (AST), or alanine transaminase (ALT) ≥2 × upper limit of normal (ULN)
   - Alkaline phosphatase (ALP) or gamma-glutamyl transferase (GGT) ≥3 × ULN
   - Abnormal renal function defined as glomerular filtration rate ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation)[8]
4. An acute upper or lower respiratory infection, PEx, 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.

- 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.

6. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug (Day 1).
7. Ongoing or prior participation in an investigational drug study (including studies investigating ELX with or without coadministration with other study drugs) within 28 days of the Screening Visit.
   - A washout period of 5 terminal half-lives of the previous investigational study drug, or **28** 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.
8. Use of restricted medication within specified duration before the first dose of study drug as defined in Table 9-2.
9. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study.
10. **Part B only**: Elevated serum ALT or AST ≥3 × ULN or total bilirubin ≥2 × ULN in the previous year.

9 STUDY IMPLEMENTATION

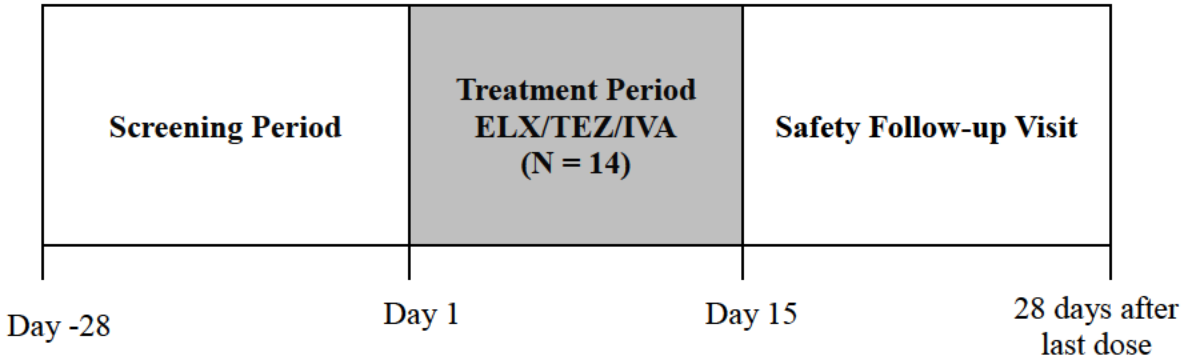
9.1 Study Design

This is a Phase 3, 2-part (Parts A and B), multicenter study evaluating the safety, tolerability, PK, PD, and efficacy of ELX/TEZ/IVA in CF subjects 2 through 5 years of age (inclusive).

Part A

A schematic of the study design for Part A is provided in Figure 9-1. Approximately 14 subjects (F/F or F/MF genotypes) will be enrolled. During the Treatment Period, subjects will be administered ELX/TEZ/IVA for approximately 15 days (Table 9-1). Safety, tolerability, and available PK data from Part A will be reviewed by Vertex to confirm or adjust the dose(s) chosen for Part B. Additional subjects may be enrolled as needed in Part A, based on emerging PK data, in order to provide sufficient information to select the dose(s) for Part B. Subjects who participate in Part A may participate in Part B.

Figure 9-1 VX20-445-111 Part A Study Design



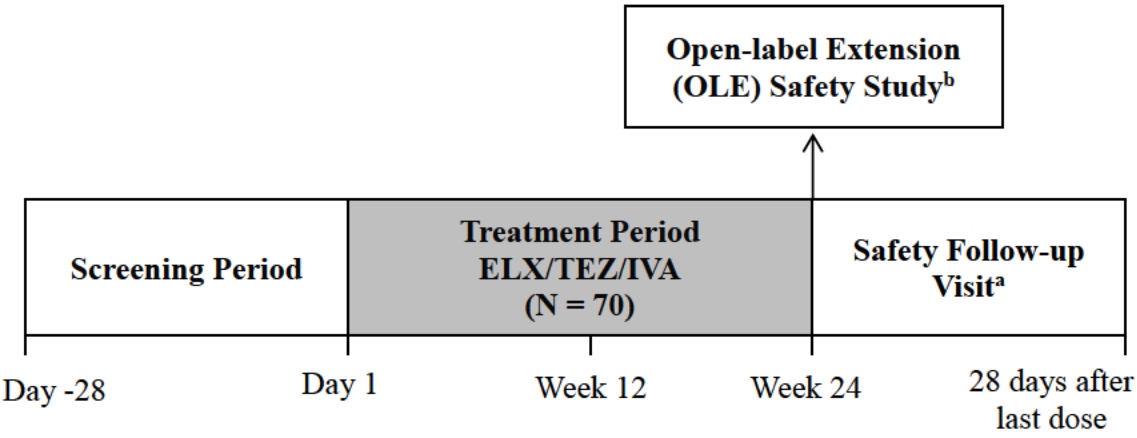
ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor
Note: ELX/TEZ/IVA will be administered from Day 1 through Day 15. On Day 15, only the morning dose will be administered.

Part B

A schematic of the study design for Part B is provided in Figure 9-2. Part B will initiate after available data from Part A has been reviewed by Vertex and the Part B dose(s) has been confirmed or adjusted. Part B will enroll approximately 70 subjects, of which at least 30 subjects will have F/MF genotypes and at least 15 subjects with the F/F genotype. At least 25 subjects should be between 2 and 3 years of age (inclusive). During the Treatment Period, subjects will be administered ELX/TEZ/IVA (Table 9-1) for approximately 24 weeks.

Subjects who are eligible will be offered the opportunity to enroll in an open-label extension (OLE) safety study.

Figure 9-2 VX20-445-111 Part B Study Design



ELX: elexacaftor; IVA: ivacaftor; OLE: open-label extension; TEZ: tezacaftor
[a] The Safety Follow-up Visit is not required for subjects who enroll in an OLE safety study within 28 days of the last scheduled visit in the Treatment Period.
[b] Subjects who are eligible will be offered the opportunity to enroll in an OLE safety study evaluating ELX/TEZ/IVA.

Table 9-1 Parts A and B Doses

Subject Weight at Day 1	ELX Dose	TEZ Dose	IVA Dose
Part A			
≥14 kg only	100 mg qd	50 mg qd	75 mg q12h
Part B			
≥14 kg	100 mg qd	50 mg qd	75 mg q12h
≥10 kg to <14 kg	80 mg qd	40 mg qd	60 mg qAM 59.5 mg qPM

ELX: elexacaftor; IVA: ivacaftor; qAM: once every morning; qd: once daily; qPM: once every evening; q12h: every 12 hours; TEZ: tezacaftor

9.1.1 Screening

Screening Visit assessments are listed in Table 3-1 (Part A) and Table 3-3 (Part B).

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

Subjects who participate in Part A may participate in Part B. Subjects from Part A will be screened for Part B and must be deemed eligible before enrolling in Part B.

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

Part A

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 may qualify for the study.

Part B

Screening assessments may be repeated once to establish study eligibility, except for LFT assessment(s) if LFT values at the original Screening Visit were elevated (total bilirubin, AST, or ALT ≥2 × ULN). If repeat values of the individual assessment(s) are within the eligibility criteria and completed within the screening window, then the subject may qualify for the study. Repetition of LFT screening assessment(s) that do not meet eligibility criteria is not permitted, with the following exceptions:

- If there is clear evidence of a laboratory error or equipment malfunction, then collection of a repeat sample for the appropriate laboratory test may be permitted after discussion with the Vertex medical monitor or authorized designee.
- If an acute non-CF etiology is identified for elevated transaminases, exclusionary LFT levels may be retested within 2 weeks of the original Screening Visit date.

If the repeat values satisfy the eligibility criteria and have been completed within the screening window or extended screening window (Section 9.1.1.3), then the results can be considered qualifying for the study.

9.1.1.2 Rescreening

Subjects may be rescreened once. If a subject is rescreened, the subject will provide informed consent and assent (as applicable), and all screening assessments will be repeated, except for:

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

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

In Part B, rescreening is not allowed if the LFT values obtained at the original Screening Visit and retesting (if applicable) were exclusionary (i.e., total bilirubin, AST, or ALT ≥2 × ULN).

9.1.1.3 Extension of Screening Period Window

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

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

9.1.2 Treatment Period

Treatment Period assessments are listed in Table 3-2 (Part A) and Table 3-4 (Part B).

The Treatment Period will last approximately 15 days in Part A and 24 weeks in Part B. 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 assessments for all study visits, as described in Section 9.1.4.

9.1.3 Follow-up

The Safety Follow-up Visit is scheduled to occur 28 (± 7) days after the last dose of study drug. The Safety Follow-up Visit is not required for Part B subjects who complete the Week 24 Visit and enroll in the OLE safety study within 28 days after the last dose of study drug.

9.1.4 Early Termination of Treatment

If a subject prematurely discontinues study drug treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the decision to discontinue treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit (Table 3-2 for Part A and Table 3-4 for Part B), if applicable (Section 9.1.3).

If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit.

Subjects who prematurely discontinue study drug treatment will continue to complete all scheduled study visits for assessments following completion of the ETT Visit, as detailed in Table 3-4.

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 (Section 9.9).

9.1.5 Lost to Follow-up

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

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

9.1.6 Completion of Study Participation

Completion of study participation for each individual subject is defined as 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)

Part B

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

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

The end of study is defined in Section 13.2.9.

9.1.7 Data Monitoring Committee

Safety and tolerability data will be reviewed by a data monitoring committee (DMC) to ensure the safety of the subjects (Section 12.5). Procedural details of the DMC's structure and function, frequency of meetings, and data planned for review will be in the DMC charter. The DMC charter will be finalized before the first subject is screened.

9.1.8 Use of Remote Measures in Extenuating Circumstances

Study visits should be performed in the clinic as specified in Table 3-2 and Table 3-4, if at all possible. However, under extenuating circumstances, remote measures may be implemented (e.g., if a subject is unable to travel to the study site due to safety concerns and/or local restrictions related to COVID-19 or other emerging events). The decision whether to conduct a study visit remotely or in clinic will be at the discretion of the investigator; if the investigator determines that study visits will be conducted remotely, the medical monitor should be notified. The Screening visits (including initial consent) and Day 1 visits must be performed in the clinic.

Whenever local regulations or site practice do not allow remote measures, visits will be conducted at the site.

The following remote measures may be implemented. Additional details can be found in the Study Reference Manual.

- Reconsent may be obtained remotely in writing (or verbally, with follow-up written confirmation), as allowed by local regulations.
- Study drug may be shipped directly from the site to the subject, as applicable and as allowed by local regulations.
- Study visits (except at Screening and Day 1) may be conducted as in-home visits by qualified personnel.
- Study assessments may be performed or overseen by qualified personnel conducting the in-home visits, except for MBW assessments.
- Remote monitoring visits may be implemented as applicable (including remote source data verification) and as allowed per local regulations.

9.2 Method of Assigning Subjects to Treatment Groups

This is an open-label study.

9.3 Rationale for Study Elements

9.3.1 Study Design

This open-label study is designed to evaluate the PK and safety of ELX/TEZ/IVA in this pediatric CF population and confirm the doses and appropriate weight cut-off. The design is consistent with ICH guidelines for the study of human subjects, especially children, and balances safety concerns with potential benefits for the individual.

9.3.2 Study Population

This study will enroll CF subjects 2 through 5 years of age (inclusive). Part A will enroll CF subjects with F/MF or F/F genotypes. Part B will enroll CF subjects who have at least 1 *F508del* mutation in the *CFTR* gene or an ELX/TEZ/IVA-responsive *CFTR* mutation as listed in Appendix B. ELX/TEZ/IVA is expected to provide clinical benefit to these patients based on the results of Phase 3 studies (Studies VX17-445-102 and VX17-445-103), which demonstrated the efficacy and safety of ELX/TEZ/IVA in CF subjects ≥12 years of age who have F/MF and F/F genotypes. A pivotal study of ELX/TEZ/IVA in CF subjects 6 through 11 years of age (inclusive; VX18-445-106) demonstrated efficacy and safety similar to results seen in CF subjects ≥12 years of age.

Given the progressive nature of CF, there is a strong rationale for treating patients earlier in life. Experience with other CFTR modulators in pediatric subjects 2 through 5 years of age, including LUM/IVA and IVA, suggests that the safety profile of ELX/TEZ/IVA will be similar in children and adults, which supports evaluation of ELX/TEZ/IVA in pediatric subjects in the present study.

9.3.3 Study Drug Dose and Duration

An ELX dose of 200 mg once daily (qd) in TC with TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) was evaluated in pivotal Phase 3 studies of adult and adolescent (≥12 years of age) CF subjects with F/MF and F/F genotypes. These studies demonstrated that treatment with this ELX/TEZ/IVA regimen resulted in rapid, robust, clinically meaningful, and statistically significant improvements in all primary and key secondary efficacy and PD endpoints.

TC regimens of ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h and ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h were evaluated in a Phase 3 study of pediatric (6 to <12 years of age) CF subjects with F/MF and F/F genotypes. This study demonstrated safety and efficacy similar to results seen in CF subjects ≥12 years of age.

Part A

The TC regimen of ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h selected for evaluation in Part A is the same dose studied in lower weight 6 to <12 year old subjects, and was based on population PK modeling. This modeling used TC data from CF subjects ≥6 years of age and simulated exposures for body weights typical of the 2- to <6-year-old population. The simulations indicated that the proposed dosing regimen for Part A is predicted to provide ELX, TEZ, and IVA exposures similar to those shown to be safe and efficacious in adults from Phase 3 studies.

Part B

For Part B, subjects will be administered either ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h or ELX 80 mg qd/TEZ 40 mg qd/IVA 60 mg once every morning (qAM) and 59.5 mg once every evening (qPM). The appropriate weight cut-off for the switch between these regimens was determined based on population PK modeling that included PK data from Part A and additional PK data from TC studies conducted in CF subjects ≥6 years of age.

Duration of Dosing

The 15-day duration of dosing in Part A provides an adequate assessment PK, safety, and tolerability of ELX/TEZ/IVA before exposing subjects to a longer treatment duration of 24 weeks in Part B.

9.3.4 Rationale for Study Assessments

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. Baseline and follow-up ophthalmologic examinations are recommended for monitoring of pediatric patients treated with IVA-containing drug regimens, and have been added to the standard safety assessments.

[redacted]

LCI is a measure of ventilation inhomogeneity assessed by multiple-breath washout (MBW) that is based on tidal breathing techniques that have been evaluated in patients as young as infants.[9, 10] Studies have shown that LCI correlates with forced expiratory volume in 1 second (FEV_1) in its ability to measure airway disease and can detect lung disease at an earlier stage than spirometry.[11, 12] Furthermore, data from Study VX10-770-106 in CF patients with an FEV_1 >90% showed LCI to be a more sensitive outcome measure than FEV_1. As with spirometry testing, performing MBW assessments in young children can be difficult.[13] Therefore, only subjects who are ≥3 years of age at screening will undergo the MBW assessments in Part B.

[redacted]

9.4 Study Restrictions

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

Table 9-2 Prohibited Medications

	Timing of Restriction		
Medication	**Start of Restriction**	**End of Restriction**	**Rationale**
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through completion of study participation	ELX, TEZ, and IVA are metabolized extensively via CYP3A4. Therefore, use of moderate and strong inducers and inhibitors of CYP3A, which have the potential to alter the exposure of ELX, TEZ, or IVA, are 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	
CFTR modulators (investigational or approved), except for study drugs	None allowed within 28 days before the first dose of the study drug on Day 1	None allowed until after the last dose of study drug	These agents may confound the results of this study.

CYP: cytochrome P450; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

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

9.5 Prior and Concomitant Medications

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

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

- Subjects should remain on a stable treatment regimen for their CF from 28 days before the Day 1 Visit through completion of study participation. Stable treatment regimen is defined as the current treatment regimen for CF that subjects have been following for at least 28 days before the Day 1 Visit. Subjects should not initiate long-term treatment with new medication from 28 days before the Day 1 Visit through completion of study participation. Guidelines for stable treatment regimens for CF are as follows:
    - Subjects who are taking inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
    - Subjects who cycle onto and off of an inhaled antibiotic should continue on their prior schedule. The timing of the first dose of study drug on the Day 1 Visit should be synchronized as closely as possible (e.g., not more than ± 3 days) to the first day in the cycle onto the inhaled antibiotic.
    - Subjects who alternate between 2 different inhaled antibiotics should remain on the same cycling schedule during the study. The timing of the first dose of study drug on the Day 1 Visit should be synchronized as closely as possible (e.g., not more than ± 3 days) to the first day in the cycle onto 1 of the inhaled antibiotics.
- Subjects may receive doses of prednisone or prednisolone of up to 10 mg/day chronically, or up to 60 mg daily for up to 5 days.
- ELX may inhibit OATP1B1 and OATP1B3, which may increase the exposure of medicinal products that are substrates for these transporters. Substrates such as statins, glyburide, nateglinide, and repaglinide should be used with caution.
- IVA is a weak inhibitor of P-glycoprotein (P-gp). Administration of IVA may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. Digoxin or other substrates of P-gp with a narrow therapeutic index, such as cyclosporine, everolimus, sirolimus, and tacrolimus, should be used with caution and appropriate monitoring.
- IVA may inhibit CYP2C9; therefore, during coadministration with warfarin, additional monitoring of the international normalized ratio is recommended. Other medicinal products that are CYP2C9 substrates for which exposure may be increased include glimepiride and glipizide; these should be used with caution.
- Information about bronchodilator use during the study will be collected and documented. Subjects who are using a bronchodilator should have their MBW assessments performed according to the guidelines provided in Section 11.4.2.

9.6 Administration

9.6.1 Dosing

Study drug will be orally administered with the approved foods and liquids listed in the Study Manual (e.g., apple sauce). The doses to be administered are shown in Table 9-1.

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

1. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed.
2. All doses of study drug (morning and evening, as applicable) should be administered at approximately every 12 hours (± 1 hour for **Part A** and ± 2 hours for **Part B**) on each dosing occasion. For example, 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 for **Part A**, and between 06:00 hour and 10:00 hour for **Part B**.
3. At the Day 1 Visit, all subjects will be observed for 4 hours after the morning dose of the study drug.
4. 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.
5. For visits after the Day 1 Visit, subjects will be instructed to bring all used and unused study drug to the site; study drug will be dispensed at each visit, as appropriate.
6. **Part A:** At the Day 15 Visit, only the morning dose of study drug will be administered.

   Part B: At the Week 24 Visit, the morning dose of study drug will NOT be administered. The last dose of study drug will be the evening dose administered the day before the Week 24 Visit.

9.6.2 Missed Doses

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

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

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

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

9.7 Dose Modification for Toxicity

No dose modifications for toxicity are allowed. If any unacceptable toxicity arises, individual subjects will discontinue dosing (Section 9.1.4).

9.8 Study Drug Interruption and Stopping Rules

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

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

9.8.1 Liver Function Tests

The central laboratory will notify the medical monitor of 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

Individuals who develop a generalized rash will be monitored closely. Study drug dosing should be interrupted if a subject develops a generalized rash of Grade 3 or higher (Section 13.1.1.4), or a rash that is considered a serious adverse event (SAE). The investigator will notify the medical monitor of any rash that results in interruption of study drug, is Grade 3 or higher (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

Subjects (or subjects' parent/legal guardian) may withdraw from the study at any time at their own request. Subjects may be withdrawn at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance (study drug dosing or study procedures), or administrative reasons. A subject who withdraws (or is withdrawn by parent/legal guardian) from study drug treatment will continue to be followed unless the subject (or parent/legal guardian) withdraws consent.

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)

Subjects who discontinue study treatment early should continue to 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 a Safety Follow-up Visit, if applicable (see Section 9.1.4), and follow up with the subject regarding any unresolved AEs.

If a subject withdraws consent for the study, no further assessments will be performed. Vertex may retain and continue using the study data and samples after the study ends, and may use the samples and information in the development of the study compound, for other drugs and diagnostics, in publications and presentations, and for education purposes. If a subject withdraws from the study, the study data and samples collected will remain part of the study. A subject will not be able to request the withdrawal of his/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

Subjects who withdraw or are withdrawn for nonsafety reasons during the study drug Treatment Period may be replaced as needed in Part A, based on emerging PK data, to confirm the dose(s) for Part B.

Part B

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

10 STUDY DRUG INFORMATION AND MANAGEMENT

10.1 Preparation and Dispensing

Study drug may be dispensed only under the supervision of the investigator or an authorized designee and only for administration to the study subjects. An interactive web response system (IWRS) will be used to dispense dosage based on subject weight.

10.2 Packaging and Labeling

Study drug granules will be supplied in capsules in bottles in Part A and in sachets in Part B 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

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. To ensure adequate records, all study drugs will be accounted for as described in Section 10.4 or via the drug accountability forms as instructed by Vertex.

Detailed instructions regarding the storage, handling, and dispensation of the study drug will be provided in the Pharmacy Manual.

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

	Study Drug Strength		
Drug Name, Dosing Form, Route	**Part A: All Subjects**	**Part B: Subjects ≥10 kg to <14 kg at Day 1**	**Part B: Subjects ≥14 kg at Day 1**
ELX/TEZ/IVA, FDC granules, oral			
ELX	100 mg	80 mg	100 mg
TEZ	50 mg	40 mg	50 mg
IVA	75 mg	60 mg	75 mg
IVA, granules, oral	75 mg	59.5 mg	75 mg

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

10.4 Drug Accountability

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

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

10.5 Disposal, Return, or Retention of Unused Drug

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

The principal investigator, study site staff, including pharmacy personnel will assist Vertex with any recall activities (as applicable) and place impacted investigational medicinal product (IMP) in quarantine when requested.

10.6 Compliance

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

If a subject's parent or legal guardian demonstrates continued noncompliance of study drug dosing despite educational efforts, the investigator should consider discontinuing the subject from the study.

10.7 Blinding and Unblinding

This will be an open-label study; however, subjects and their parent or legal guardian should not be informed of their study-related LCI, SwCl, [redacted] results during the Treatment Period (Part B only), regardless if the subject permanently discontinues treatment.

11 ASSESSMENTS

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

11.1 Subject and Disease Characteristics

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

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

11.2 Pharmacokinetics

11.2.1 Blood Sampling

Blood samples will be collected to determine plasma concentrations of ELX, TEZ, IVA, and relevant metabolites.

Acceptable windows for sampling times are shown in Table 11-1. Samples collected outside of these acceptable windows will be considered protocol deviations.

Actual sampling times may change upon agreement between the clinical pharmacologist and investigator, but the number of samples will remain the same. All efforts will 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. The exact time of the sample collection will be noted.

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

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

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

11.2.2 Processing and Handling of Pharmacokinetic Samples

Detailed procedures for the collection of blood samples and further procedures for processing and handling of samples for PK analysis will be in the Laboratory Manual.

11.2.3 Bioanalysis

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

[redacted]

11.4 Efficacy and Pharmacodynamics (Part B Only)

11.4.1 Sweat Chloride

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

11.4.2 Multiple-breath Washout

The N_2-MBW testing will be performed in multiple replicates for subjects ≥3 years of age at screening and at time points noted in Table 3-4, and the final LCI value will be calculated from

the technically acceptable washout replicates by a central reader. The final LCI value at each visit will be the value provided by the LCI vendor based on the replicates.

Pre-bronchodilator MBW is defined as MBW 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 MBW test;
- withheld their long-acting bronchodilator (e.g., salmeterol) for more than 12 hours before the MBW test; and
- withheld their once-daily, long-acting bronchodilator (e.g., tiotropium bromide [Spiriva®]) for more than 24 hours before the MBW test.

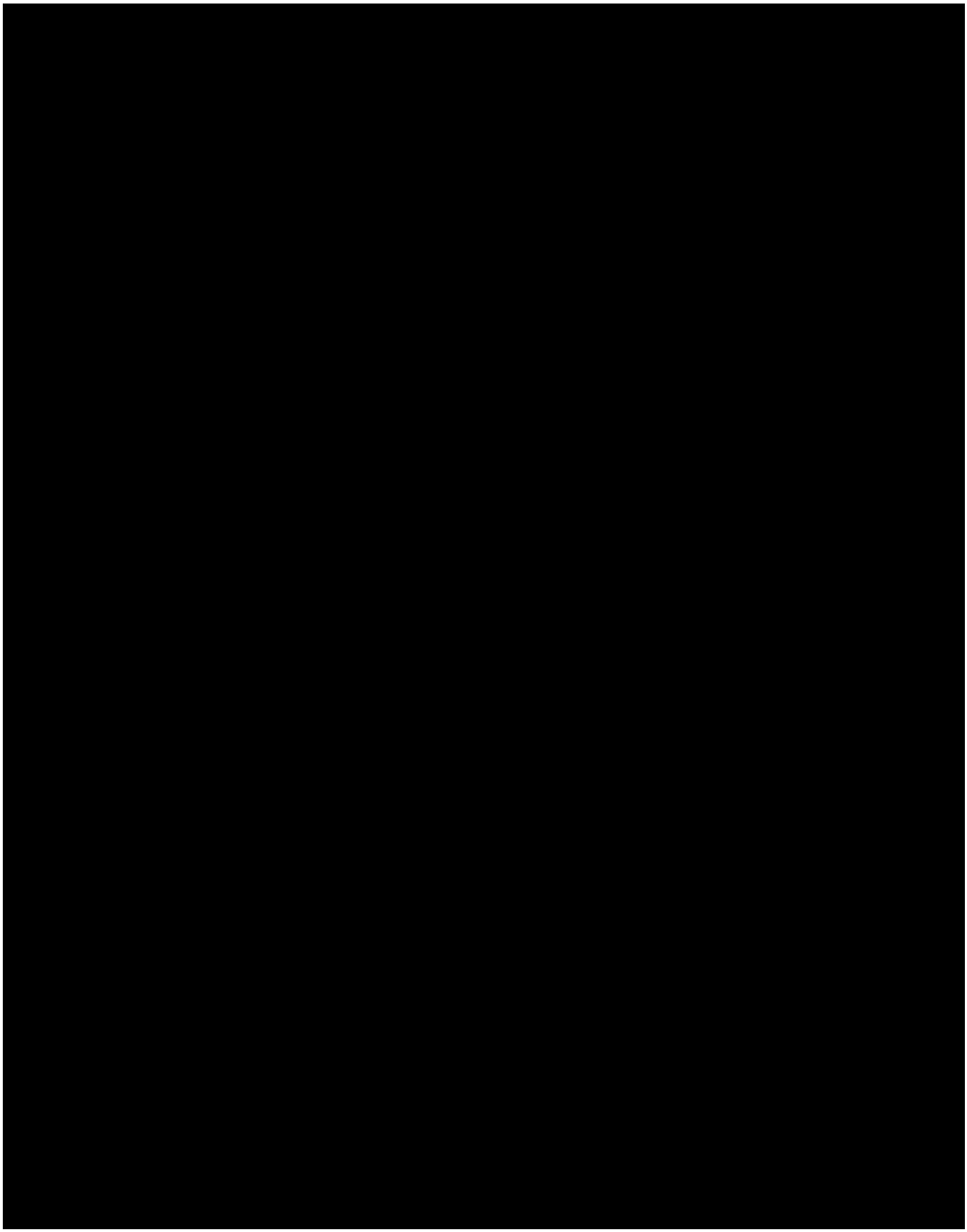
During the Screening Period, the MBW test may be performed pre- or post-bronchodilator. At all other visits, all MBW tests should be performed pre-bronchodilator. During the Treatment Period, MBW testing must be performed before study drug dosing (Section 9.6.1) at approximately the same time at each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

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

Subjects and parents/legal guardians should not be informed of study-related LCI results.

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

[redacted]



11.5 Safety

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. PEs 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

All AEs will be assessed, documented, and reported in accordance with current ICH E6 GCP Guidelines. Section 13.1 outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting AEs. Electronic AE case report form (CRF) completion guidelines for investigators as well as training will be provided.

11.5.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory. A local laboratory may be used for the Week 20 (Part B) assessments if the subject cannot return to the site for a blood draw. All blood samples will be collected while subjects are in a seated or supine position. To minimize the total amount of blood taken during screening and at Day 1, a single set of pre-dose hematology and coagulation assessments will be obtained from a blood draw taken up to 9 days before Day 1 dosing in Part B. Screening serum chemistry assessments must also be obtained from a blood draw taken up to 9 days before Day 1 dosing in Part B. Serum chemistry will also be drawn prior to study drug dosing on Day 1. Specific instructions for the collection, processing, and shipment for centrally drawn samples will be provided in a separate Laboratory Manual. Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

The safety laboratory test panels are shown in Table 11-2.

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
Phosphate	Neutrophils	Urine glucose
Total bilirubin, direct bilirubin, indirect bilirubin	Lymphocytes	
Alkaline phosphatase	Monocytes	
Aspartate transaminase	**Coagulation**	
Alanine transaminase	Activated partial thromboplastin time	
Amylase	Prothrombin time	
Lipase	Prothrombin time International Normalized Ratio	
Gamma-glutamyl transferase		
Protein		
Albumin		
Creatine kinase		
Cholesterol		

[a] If urinalysis results are positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be done, and results will be provided for leukocytes, erythrocytes, crystals, bacteria, and casts.
[b] If blood urea nitrogen cannot be collected, urea may be substituted.

CF genotype (Screening Period only): CF genotyping will be performed on all subjects. 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 and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9). This assessment does not need to be repeated in the case of rescreening or for confirmed subjects in Part A who wish to participate in Part B.

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

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

11.5.3 Physical Examinations and Vital Signs

A PE of all body systems and vital signs assessment will be performed at 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.

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

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

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

11.5.4 Electrocardiograms

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

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

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

To ensure 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.

11.5.5 Ophthalmologic Examination

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

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

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

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.

Part B Only

In addition to the screening ophthalmologic examination, all subjects who have completed at least 12 weeks of study drug treatment will have a single follow-up ophthalmologic examination. This examination should be completed at or up to 4 weeks before the Week 24 Visit, unless the subject prematurely discontinues study drug, in which case this examination should occur by the Safety Follow-up Visit (or ETT Visit for subjects who do not complete a Safety Follow-up Visit), as described in Table 3-4.

11.5.6 Contraception and Pregnancy

Not applicable.

12 STATISTICAL ANALYSIS

This section presents a summary of the principal features of the planned analyses. Statistical analysis details will be 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 clinical database lock.

12.1 Sample Size and Power

Part A

Approximately 14 subjects will be enrolled in Part A. Sample size calculations were determined based on ELX and M23-445 estimates of clearance. Assuming that the variability in this age group is the same as the variability observed in adults, data from 14 subjects will allow at least 80% power to target a 95% CI within 60% and 140% of the geometric mean estimate of clearance for ELX and M23-445.

Part B

No formal power calculation is performed. The number of subjects in Part B is deemed adequate to meet the primary safety objective. The planned enrollment is approximately 70 subjects. Assuming a dropout rate of 10% or 20%, approximately 63 or 56 subjects, respectively, are expected to complete Part B. Incidence of AEs is a safety endpoint. Table 12-1 presents estimated probabilities for observing at least 1 subject with an AE for the given incidence rate (θ) and number of subjects completing Part B. The probabilities were calculated by assuming a binomial distribution for the number of AEs using SAS®.

Table 12-1 Probability of Observing At Least 1 Subject With an AE in the Study if the AE Incidence (θ) is 5% and 10%

Number of Subjects Completing Part B	θ = 5%	θ = 10%
56	94.3%	99.7%
63	96.1%	99.9%

θ: incidence; AE: adverse event

12.2 Analysis Sets

Assignment of subjects to analysis sets will be done before the clinical data lock for the study. The following analysis sets will be defined separately for Part A and Part B.

All Subjects Set

The All Subjects Set will include all subjects who are enrolled (defined as subjects having data in the clinical database) or received at least 1 dose of study drug. This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

Full Analysis Set (FAS)

The FAS will include all subjects who are enrolled (defined as subjects having data in the clinical database) and 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 and PD endpoints, unless otherwise specified.

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, unless otherwise specified.

12.3 Statistical Analysis

12.3.1 General Considerations

Data from Part A and Part B will be analyzed separately. All individual subject data will be presented in individual subject data listings.

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

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 (Section 9.1.6), whichever is earlier.

Baseline value, unless specified otherwise, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug. Details will be provided in SAP.

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

12.3.2 Background Characteristics

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, study drug exposure, compliance (Part B only), and other background characteristics will be summarized for Part A and Part B.

12.3.3 Efficacy and Pharmacodynamic Analysis

Two of the secondary objectives for Part B are to evaluate the efficacy and PD of ELX/TEZ/IVA. Principal features of the efficacy and PD analyses are presented in this section. Further details will be provided in the SAP.

12.3.3.1 Analysis of Primary Efficacy Endpoints

Not applicable as efficacy is not a primary endpoint.

12.3.3.2 Analysis of Secondary Efficacy and Pharmacodynamic Endpoints

A summary of observed values and change from baseline will be provided for all secondary efficacy endpoints based on the FAS in Part B.

- **Absolute change in SwCl from baseline through Week 24**

  Absolute change from baseline in SwCl will be analyzed using a mixed-effects model for repeated measures (MMRM) approach based on the FAS. The MMRM will be used to estimate the mean absolute change in SwCl through Week 24. The model will include absolute change from baseline in SwCl as the dependent variable, and with visit, baseline SwCl value, and genotype group as covariates. Data obtained from Week 4, Week 12, and Week 24 Visits will be included in the model. An unstructured covariance structure will be used to model the within-subject variations.

  The primary results obtained from the model will be the average treatment effect through Week 24. The estimated mean change from baseline in SwCl through Week 24, along with the corresponding 95% CI and 2-sided *P* value will be provided. The treatment effect at each post-baseline visit, obtained from the model, will be provided as well.

- **Absolute change in $LCI_{2.5}$ from baseline through Week 24**

  Analysis of this endpoint will be based on an MMRM model that is similar to the analysis of absolute change from baseline in SwCl through Week 24, with the baseline $LCI_{2.5}$ value included as a covariate instead of baseline SwCl.

12.3.3.3 Multiplicity Adjustment

No multiplicity adjustment is planned.

[redacted]

[redacted]

12.3.4 Safety Analysis

Safety is a secondary objective of Part A, and the primary objective of Part B. All safety analyses will be conducted for the Safety Set in Part A and Part B separately. The 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

12.3.4.1 Adverse Events

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

- **Pretreatment AE**: any AE that occurred before the first dose of study drug
- **TEAE**: any AE that is worsened (either in severity or seriousness) or 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 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, 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 (Section 13.1.1.4)

Summaries will be presented by 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.

12.3.4.2 Clinical Laboratory Assessments

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

The number and percentage of subjects meeting a threshold analysis criterion during the TE Period will be summarized. 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 will be listed in individual subject data listings only. In addition, a listing containing individual subject hematology, chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled visits.

12.3.4.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided, at each scheduled visit and time point, as applicable, for the following ECG interval measurements (in msec): RR, PR, QT, and QT interval corrected by Fredericia's formula (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.

12.3.4.4 Vital Signs

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.

12.3.4.5 Pulse Oximetry

For the treatment-emergent pulse oximetry measurements, a summary of observed values and change from baseline values will be provided at each 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.

12.3.4.6 Ophthalmologic Examinations

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

12.3.4.7 Physical Examination

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

12.4 Interim Analysis

Not applicable.

12.5 Data Monitoring Committee Analysis

The DMC (Section 9.1.7) will conduct periodic planned safety review(s) of study data. Details of the safety and efficacy review(s) will be described in the DMC Charter.

12.6 Clinical Pharmacology Analysis

12.6.1 Pharmacokinetic Analysis

The PK analysis of ELX, TEZ, IVA, and relevant metabolites 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.

12.6.2 Pharmacokinetic/Pharmacodynamic Analyses

PK/PD analyses may be performed on selected PD assessments, which include SwCl, $LCI_{2.5}$, as well as other endpoints such as [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 ELX, TEZ, IVA, or metabolite plasma concentrations will be used in the potential pharmacological response models to describe changes in each endpoint. Fixed- and random-effect parameter estimates and their uncertainty will be estimated.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

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

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

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

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

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

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time the ICF is signed until the following times:

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, the earliest of
    - 28 days after the last dose of study drug, or
    - the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (see Section 9.1.4)

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

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

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed September 2019). When considering the severity of an AE in a pediatric subject, the investigator will consider that reference ranges for pediatric clinical laboratory parameters may differ from those in the CTCAE. The severity of an AE described by a term that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

Classification	Description
Grade 1 (Mild)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 (Moderate)	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4 (Life-threatening)	Life-threatening consequences; urgent intervention indicated
Grade 5 (Death)	Death related to adverse event

Source: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed September 2019)
ADL: activities of daily living; AE: adverse event
Note: A semi-colon indicates 'or' within the description of the grade.

[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

13.1.1.5 Adverse Event Causality

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

Table 13-2 Classifications for AE Causality

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

13.1.1.6 Study Drug Action Taken

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

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

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

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

13.1.1.7 Adverse Event Outcome

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

Table 13-4 Classifications for Outcome of an AE

Classification	Definition
Recovered/resolved	Resolution of an AE with no residual signs or symptoms
Recovered/resolved with sequelae	Resolution of an AE with residual signs or symptoms
Not recovered/not resolved (continuing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing

Table 13-4 Classifications for Outcome of an AE

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

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

Clarification will be made between the terms "serious" and "severe" because they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event, as in mild, moderate, or severe myocardial infarction. The event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as

"serious", which is based on subject/event outcome or action described above, and is usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining expedited regulatory reporting obligations.

13.1.2.2 Reporting and Documentation of Serious Adverse Events

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

For SAEs that occur after obtaining informed consent through the Safety Follow-up Visit, the SAE Form will be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

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

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

13.1.2.3 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities, IEC, and participating investigators in accordance with current ICH E2A Guidelines and/or local regulatory requirements, as applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to central IECs.

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

13.2 Administrative Requirements

13.2.1 Product Complaints

A product complaint is defined as any verbal or written communication addressed to Vertex, or designee, of inquiry or dissatisfaction with the identity, strength, quality, or purity of a released

drug product, IMP, or medical device. In addition, suspected counterfeit/falsified product is considered a product complaint.

Product complaints are to be reported to Vertex.

13.2.2 Ethical Considerations

The study will be conducted in accordance with the current ICH E6 GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local applicable laws and regulations. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

13.2.3 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject or legal representative or guardian (if applicable), and assent will be obtained from the subject (if applicable), before study participation. The method of obtaining and documenting the informed consent and assent (if applicable) and the contents of the consent will comply with current ICH E6 GCP Guidelines and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

13.2.4 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.

13.2.5 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.

13.2.6 Subject Privacy

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

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

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

13.2.7 Record Retention

The investigator will maintain all study records according to current ICH E6 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.

13.2.8 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.

13.2.9 End of Study

The end of study is defined as the last scheduled visit (or scheduled contact) of the last subject.

13.3 Data Quality Assurance

Vertex or its designated representative will conduct a study site visit to verify the qualifications of each investigator, inspect clinical study site facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation per current ICH E6 GCP Guidelines.

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

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

13.4 Monitoring

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

The study will be monitored by Vertex or its designee. Monitoring will be done by a representative of Vertex or designee (study site monitor), who will review the CRFs/SAE Forms and source documents per current ICH E6 GCP Guidelines. The study site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

13.5 Electronic Data Capture

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

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

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

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

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

13.6 Confidentiality and Disclosure

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

The investigator understands that the information developed from this clinical study will be used by Vertex in connection with the development of the study drug and other drugs and diagnostics, and therefore may be disclosed as required to other clinical investigators, business partners and associates, the FDA, and other government agencies. The investigator also understands that, to allow for the use of the information derived from the clinical study, the investigator has the obligation to provide Vertex with complete test results and all data developed in the study.

13.7 Publications and Clinical Study Report

[redacted]

13.7.2 Clinical Study Report

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

14 REFERENCES

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APPENDIX A Eligible MF CFTR Mutations

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

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

(2) in vitro testing that supports lack of responsiveness to IVA and TEZ/IVA.

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 IVA and TEZ/IVA in the assay

Eligible MF Mutations

The mutations below are detectable by an FDA-cleared genotyping assay or other method (e.g., sequencing).

This list does 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 VX20-445-111

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

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 (G970R)	3600+2insT
405+1G>A	1249-1G>A	1811+1.6kbA>G		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		

182delT	1119delA	1782delA	2732insA	3791delC
306insA	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	
1078delT	1677delTA	2711delT	3737delA	

Non-exhaustive List of Minimal Function *CFTR* Mutations Eligible for VX20-445-111

CFTRdele1	CFTRdele16-17b	991del5
CFTRdele2	CFTRdele17a,17b	1461ins4
CFTRdele2,3	CFTRdele17a-18	1924del7
CFTRdele2-4	CFTRdele19	2055del9>A
CFTRdele3-10,14b-16	CFTRdele19-21	2105-2117del13insAGAAA
CFTRdele4-7	CFTRdele21	2372del8
CFTRdele4-11	CFTRdele22-24	2721del11
CFTR50kbdel	CFTRdele22,23	2991del32
CFTRdup6b-10	124del23bp	3121-977_3499+248del2515
CFTRdele11	306delTAGA	3667ins4
CFTRdele13,14a	602del14	4010del4
CFTRdele14b-17b	852del22	4209TGTT>AA

A46D	V520F	Y569D	N1303K
G85E	A559T	L1065P	
R347P	R560T	R1066C	
L467P	R560S	L1077P	
I507del	A561E	M1101K	

CFTR: cystic fibrosis transmembrane conductance regulator gene

Source: CFTR2.org. 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.

[a] Also known as 2183delAA>G.

APPENDIX B Eligible ELX/TEZ/IVA-Responsive CFTR Mutations

As described in Section 8.1, in Part B, subjects with at least 1 *F508del* mutation in the *CFTR* gene or an ELX/TEZ/IVA-responsive *CFTR* mutation based on in vitro data, qualify to be screened for the study. The list of qualifying ELX/TEZ/IVA-responsive *CFTR* mutations is presented below.

CFTR Mutations Responsive to ELX/TEZ/IVA Based on In Vitro Data

3141del9	G126D	R334L	S549R	H939R	W1098C
546insCTA	H139R	R334Q	G551D	S945L	F1099L
P5L	I148T	I336K	G551S	M952I	M1101K
S13F	M152V	T338I	R553Q	M952T	I1139V
L15P	Y161D	S341P	A554E	L967S	D1152H
G27R	Y161S	L346P	V562I	G970D	V1153E
R31L	L165S	R347H	Y563N	S977F	S1159F
A46D	R170H	R347L	P574H	D979V	S1159P
E56K	I175V	R347P	F575Y	I980K	R1162L
E60K	G178E	A349V	G576A	L997F	V1240G
P67L	G178R	R352Q	G576A;R668C †	A1006E	G1244E
R74Q	F191V	R352W	D579G	Y1014C	G1249R
R74W	D192G	Q359R	E588V	F1016S	S1251N
R74W;V201M †	E193K	W361R	S589N	I1027T	S1255P
R74W;V201M;D1270N †	G194R	S364P	I601F	Y1032C	I1269N
R74W;D1270N †	G194V	E403D	D614G	T1036N	D1270N
R75Q	H199Y	D443Y;G576A;R668C †	I618T	F1052V	W1282R
G85E	V201M	D443Y	G622D	T1053I	R1283M
E92K	P205S	L453S	G628R	H1054D	R1283S
Q98R	L206W	A455E	R668C	K1060T	Q1291R
Y109N	V232D	V456A	S737F	G1061R	V1293G
D110E	A234D	V456F	R751L	R1066H	L1324P
D110H	Q237E	G463V	V754M	A1067T	L1335P
E116K	Q237H	E474K	R792G	G1069R	G1349D
R117C	R258G	G480C	I807M	R1070Q	I1366N
R117G	M265R	S492F	E822K	R1070W	H1375P
R117H	F311del	I502T	D836Y	F1074L	L1480P
R117L	F311L	F508C	S912L	L1077P	
R117P	G314E	F508C;S1251N †	D924N	H1085P	
A120T	L320V	S549N	R933G	H1085R	

† Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX20-445-111	Version #: 3.0	Version Date: 21 October 2021
Study Title: A Phase 3 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Elexacaftor/Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 Through 5 Years of Age		

15.2 Investigator Signature Page

Protocol #: VX20-445-111	Version #: 3.0	Version Date: 21 October 2021
Study Title: A Phase 3 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Elexacaftor/Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 Through 5 Years of Age		

I have read Protocol VX20-445-111, Version 3.0, and agree to conduct the study according to its terms. I understand that all information concerning elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date