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VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3 Double-blind, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of ELX/TEZ/IVA in Cystic Fibrosis Subjects 6 Years of Age and Older With a Non-*F508del* ELX/TEZ/IVA-responsive *CFTR* Mutation

Vertex Study Number: VX21-445-124

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Date of Protocol: 21 April 2022 (Version 3.0)

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Summary of Changes to the Protocol

The previous version of this protocol (Version 2.0, 24 January 2022) was amended to create the current version (Version 3.0, 21 April 2022). The protocol history is provided below.

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.0, 12 October 2021	Original version
Version 2.0, 24 January 2022	Additional ELX/TEZ/IVA-responsive mutations were added to the list of qualifying *CFTR* mutations.
Version 3.0, 21 April 2022	Current version

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

Change and Rationale	**Affected Sections**
The range of qualifying $ppFEV_1$ values was expanded to broaden the eligible population. Specifically, the maximum $ppFEV_1$ value was increased from 90% to 100%.	Section 8.1, Inclusion Criterion 6
Specified that up to 10% of subjects may be enrolled with a screening $ppFEV_1$ value >90% and ≤100% (approximately 27 subjects).	Sections 2 and 9.1
For the exclusion criterion related to medical history, a history of hypersensitivity to any component of the investigational drug product or placebo was added to the list of clinical conditions that might confound the results of the study or pose an additional risk in administering study drug(s) to the subject.	Section 8.2, Exclusion Criterion 1
Blood sample volumes to be drawn at each study visit are presented in Appendix B	Section 16

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

2 PROTOCOL SYNOPSIS

Title A Phase 3 Double-blind, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of ELX/TEZ/IVA in Cystic Fibrosis Subjects 6 Years of Age and Older With a Non-*F508del* ELX/TEZ/IVA-responsive *CFTR* Mutation

Brief Title Evaluation of Efficacy and Safety of ELX/TEZ/IVA in Subjects Without an *F508del* Mutation

Clinical Phase and Clinical Study Type Phase 3 efficacy and safety

Objectives

Primary Objective:
To evaluate the efficacy and pharmacodynamics (PD) of ELX/TEZ/IVA

Secondary Objective:
To evaluate safety and tolerability of ELX/TEZ/IVA

Endpoints

Primary Endpoint:

- Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) through Week 24

Secondary Endpoints:

- Absolute change from baseline in sweat chloride (SwCl) through Week 24
- Absolute change from baseline in Cystic Fibrosis Questionnaire - Revised (CFQ-R) respiratory domain (RD) score through Week 24
- Absolute change from baseline in body mass index (BMI) at Week 24
- Absolute change from baseline in weight at Week 24
- Number of pulmonary exacerbations (PEx) through Week 24
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry

Other Endpoints:

- Absolute change from baseline in BMI z-score (subjects ≤20 years of age) at Week 24
- Absolute change from baseline in weight z-score (subjects ≤20 years of age) at Week 24
- Plasma PK parameters including ELX, TEZ, IVA, and relevant metabolites

Number of Subjects Approximately 270 subjects will be enrolled in the study with up to approximately 30 subjects per *CFTR* mutation. Up to 10% of subjects may be enrolled with a screening $ppFEV_1$ value >90% and ≤100% (approximately 27 subjects).

Study Population Male and female CF subjects 6 years of age and older with at least 1 non-*F508del,* ELX/TEZ/IVA-responsive *CFTR* mutation

Investigational Drug

Active substance: ELX (VX-445)/TEZ (VX-661)/IVA (VX-770)
Activity: ELX and TEZ are CFTR correctors; IVA is a CFTR potentiator
Strength and route of administration: ELX/TEZ/IVA fixed-dose combination (FDC) tablets for oral administration at the following strengths:

- ELX 100 mg/TEZ 50 mg/IVA 75 mg
- ELX 50 mg/TEZ 25 mg/IVA 37.5 mg

Active substance: IVA (VX-770)
Activity: CFTR potentiator
Strength and route of administration: IVA tablets for oral administration at the following strengths:

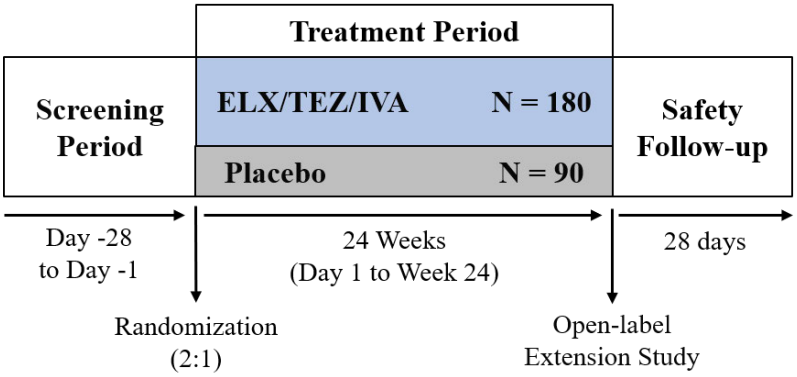
- IVA 150 mg
- IVA 75 mg

Study Duration The total study duration is approximately 32 weeks (4 weeks for the Screening Period, 24 weeks for the Treatment Period, and 4 weeks for the Safety Follow-up Period).

Study Design This is a Phase 3, randomized, placebo-controlled, double-blind, parallel group study. Subjects 6 years of age and older with a qualifying non-*F508del* ELX/TEZ/IVA-responsive *CFTR* mutation and no exclusionary mutations may be eligible for enrollment. Qualifying ELX/TEZ/IVA-responsive mutations can be categorized as minimal function (MF)-like and residual function (RF)-like. MF-like mutations have a clinical phenotype without evidence of residual CFTR function. RF-like mutations result in residual CFTR function. Exclusionary mutations are indicated for IVA in the EU label regardless of the mutation on the second allele.

Subjects will be randomized 2:1 (ELX/TEZ/IVA group: placebo group). Randomization will be stratified based on $ppFEV_1$ determined during the Screening Period (<70 versus ≥70), age at the Screening Visit (<18 years old versus ≥18 years old) and *CFTR* genotype (contains ≥1 RF-like mutation versus does not contain an RF-like mutation).

Figure 2-1 Study VX21-445-124 Design



The ELX/TEZ/IVA dose regimen will be based on the subject's age and weight on Day 1 as shown in Table 2-1; subjects will receive this dose regimen throughout the Treatment Period, regardless of changes in age or weight.

Table 2-1 Treatment Period Dosages

Treatment Group Subject Age Weight	ELX Dosage	TEZ Dosage	IVA Dosage
ELX/TEZ/IVA			
≥12 years			
All weights	200 mg qd	100 mg qd	150 mg q12h
≥6 to <12 years			
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
<30 kg	100 mg qd	50 mg qd	75 mg q12h
Placebo			
All ages and all weights	0 mg	0 mg	0 mg

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

ELX/TEZ/IVA will be administered as 2 FDC tablets in the morning and a single IVA monotherapy tablet in the evening regardless of dosing regimen.

Assessments

Efficacy and PD assessments: spirometry, CFQ-R, sweat chloride, weight, height, and PEx
Safety assessments: AEs, clinical laboratory assessments, ECGs, vital signs, pulse oximetry, physical examinations, and ophthalmologic examinations (for subjects <18 years of age on the date of informed consent)
PK assessments: Plasma PK concentrations of ELX, TEZ, IVA, and their relevant metabolites
Exploratory assessments: RNA, plasma and serum proteins

Statistical Analyses

The primary endpoint is the absolute change from baseline in $ppFEV_1$ through Week 24. The primary null hypothesis to be tested is that the mean absolute change from baseline in $ppFEV_1$ through Week 24 is the same for the ELX/TEZ/IVA and placebo treatment groups. The null hypothesis will be tested at a 2-sided significance level of 0.05.

Assuming a within-group SD of 9 percentage points and a 10% dropout rate at Week 24, a total sample size of 270 subjects (180 subjects in the ELX/TEZ/IVA group and 90 subjects in placebo group) will have approximately 90% power to detect a difference of 4.0 percentage points for the mean absolute change from baseline in $ppFEV_1$ through Week 24 between the 2 treatment groups, based on a 2-sided 2-sample t-test at a significance level of 0.05.

The primary analysis will be based on a mixed-effects model for repeated measures (MMRM). The model will include the absolute change from baseline in $ppFEV_1$ at Day 15, Week 4, Week 8, Week 16, and Week 24 as the dependent variable; treatment group, visit, and treatment-by-visit as fixed effects; additional covariates will be included as appropriate and details will be specified in the Statistical Analysis Plan (SAP); and an unstructured covariance structure will be used to model the within-subject errors.

The primary result obtained from the model will be the estimated treatment difference through Week 24. The adjusted mean with a 2-sided 95% CI and a 2-sided *P* value will be provided.

	The safety endpoints include AEs, clinical laboratory values, ECGs, vital signs, and pulse oximetry through the Safety Follow-up Visit. The safety analysis will be descriptive only.
Independent Data Monitoring Committee	Safety and tolerability data will be reviewed by an independent data monitoring committee (IDMC) to ensure the safety of the subjects. Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be in the IDMC charter. The IDMC charter will be finalized before the first subject is screened.

3 SCHEDULE OF ASSESSMENTS

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

Table 3-1 Study VX21-445-124: Screening

Event/Assessment	Screening Visit[a] Day -28 to Day -1	Comments
Informed consent (and assent, if applicable)	X	
Demographics	X	Section 11.1
Medical history	X	Section 11.1
CFTR genotype	X	Performed for all subjects (Section 11.5.2). A subject's screening *CFTR* genotype **must** confirm eligibility before the subject is randomized.
Medications review	X	Information regarding medications taken within 56 days before the Screening Visit will be collected; Section 9.5.
Height, weight, and BMI	X	Weight and height will be measured with shoes off; Sections 11.4.4 and 11.5.3
Full physical examination	X	Section 11.5.3
Vital signs and pulse oximetry	X	Collected after the subject has been at rest for at least 5 minutes; Section 11.5.3
Standard 12-lead ECG	X	Performed prior to any procedure that may affect heart rate (e.g., blood draws) and after subject has been at rest for at least 5 minutes; Section 11.5.4
Serum FSH	X	Suspected postmenopausal female subjects only; Section 11.5.2
Serum pregnancy test	X	Female subjects 9 years of age and older, and female subjects who have undergone menarche (regardless of age), Section 11.5.2
Serum chemistry	X	Section 11.5.2
Hematology and coagulation	X	
Urinalysis	X	
Ophthalmological examination	X	Conducted by an ophthalmologist or optometrist for subjects <18 years of age on the date of initial informed consent; Section 11.5.5
Sweat chloride	X	Section 11.4.2
Spirometry	X	Performed pre- or post-bronchodilator; Section 11.4.1
Adverse events	Continuous from signing of informed consent form (ICF) through completion of study participation	Section 11.5.1

BMI: body mass index; *CFTR*: cystic fibrosis transmembrane conductance regulator gene; ECG: electrocardiogram; FSH: follicle-stimulating hormone

a Visit must be performed in clinic (Section 9.1.7)

Table 3-2 Study VX21-445-124: Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Day 1[b]	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[b] (± 5 Days)	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose of Study Drug[d]	Comments
Clinic Visit	X	X	X	X		X		X	X	X	See Section 9.1.7 for use of remote measures in extenuating circumstances.
Telephone contact or telemedicine video conference					X		X				Assess subject's status, any AEs, concomitant medications, treatments, and procedures.
Randomization	X										Section 9.2
Safety, efficacy, and other assessments											
CFQ-R	X		X	X		X		X	X	X	Completed before the start of any other assessments; Section 11.4.3
Weight and height	X	X	X	X		X		X	X	X	Measured with shoes off; Section 11.4.4
Vital signs and pulse oximetry	X	X	X	X		X		X	X	X	Performed after subject has rested for at least 5 minutes; Section 11.5.3
Standard 12-lead ECG	X	X	X	X		X		X	X	X	Performed prior to any procedure that may affect heart rate (e.g., blood draws) and after subject has rested for at least 5 minutes; Section 11.5.4

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

[b] These visits must be performed in clinic (Section 9.1.7).

[c] If the subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the decision to discontinue treatment. Subjects who prematurely discontinue treatment will continue to complete all scheduled study visits for assessments following completion of the ETT Visit.

[d] The Safety Follow-Up Visit is not required for subjects who complete the Week 24 Visit and enroll in an optional open-label extension safety study within 28 days after the last dose of study drug. If an ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit replaces the Safety Follow-up Visit.

Table 3-2 Study VX21-445-124: Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Day 1[b]	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[b] (± 5 Days)	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose of Study Drug[d]	Comments
Physical examination	Full							Full	Full		Symptom-directed physical examinations may occur at any time if deemed necessary by the investigator; Section 11.5.3
Ophthalmological examination								X at or up to 4 weeks before	X		Conducted by an ophthalmologist or optometrist for subjects <18 years of age on the date of informed consent; Section 11.5.5
Pregnancy test (female subjects of childbearing potential)	urine	serum or urine	serum or urine	serum or urine	urine (at home)	serum or urine	urine (at home)	serum or urine	serum or urine	serum or urine	Female subjects of childbearing potential are defined in Section 11.5.6.1.
Serum chemistry	X	X	X	X		X		X	X	X	Collected before the first dose of study drug on Day 1; Section 11.5.2
Hematology	X	X	X	X		X		X	X	X	
Coagulation	X							X	X	X	
PK sampling	X		X					X			Collected within 60 min before the AM dose; Section 11.2.1
Urinalysis	X							X	X	X	Section 11.5.2

Table 3-2 Study VX21-445-124: Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Day 1[b]	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[b] (± 5 Days)	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose of Study Drug[d]	Comments
Spirometry	X	X	X	X		X		X	X	X	Performed before study drug dosing. Should be performed pre-bronchodilator at approximately the same time at each visit (Section 11.4.1). If the visit is performed as a home health visit, spirometry may be performed using a mobile device (Section 9.1.7)
Sweat chloride	X	X	X	X		X		X			Section 11.4.2
Blood sample for exploratory RNA and protein analysis	X					X					Subjects weighing ≥22 kg at screening only. Section 11.3
Adverse events	Continuous from signing of ICF through completion of study participation										Section 11.5.1
Other events related to outcome	Continuous from signing of ICF through completion of study participation										Section 11.4.5
Medications review	Continuous from signing of ICF through completion of study participation										Section 9.5
Non-pharmacological treatment and procedures review	Continuous from signing of ICF through completion of study participation										
Study drug administration											
Study drug dosing	Day 1 through evening before Week 24 Visit										Section 9.6
Study drug compliance review	X	X	X	X	X	X	X	X	X	X	Section 10.6.

CFQ-R: Cystic Fibrosis Questionnaire-Revised; ECG: electrocardiogram; ETT: Early Termination of Treatment; ICF: informed consent form; PK: pharmacokinetic(s); RNA: ribonucleic acid

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List of Abbreviations

Abbreviation	Definition
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFQ-R RD	Cystic Fibrosis Questionnaire- Revised respiratory domain
CFTR	cystic fibrosis transmembrane conductance regulator gene
CI	confidence interval
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
EDC	electronic data capture
etc.	et cetera
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
FEV_1	forced expiratory volume in 1 second
FRT	Fischer Rat Thyroid
FSH	follicle-stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLI	Global Lung Function Initiative
GPS	Global Patient Safety
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board

Abbreviation	Definition
IXRS	interactive response system in which X represents voice or web, such as IWRS
max	maximum value
MF	minimal function
min	minimum value
MMRM	mixed-effects model for repeated measures
P	probability
PD	pharmacodynamic, pharmacodynamics
PE	physical examination
PEx	pulmonary exacerbations
P-gp	P-glycoprotein
PK	pharmacokinetic, pharmacokinetics
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
QTcF	QT interval corrected by Fridericia's formula
RF	residual function
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SwCl	sweat chloride
TE	Treatment-emergent
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
USA	United States of America

5 INTRODUCTION

5.1 Background

Cystic fibrosis (CF) is a rare autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality for which there is currently no cure. CF affects more than 80,000 individuals worldwide[1-4], including more than 49,000 individuals in the EU.[2]

CF is caused by decreased quantity and/or function of the CFTR protein due to mutations in the *CFTR* gene.[5] CFTR is an ion channel that regulates the flow of chloride and other ions across epithelia in various tissues, including the lungs, pancreas and other gastrointestinal organs, and sweat glands.[6] Decreased CFTR quantity or function results in the failure to regulate chloride transport in these tissues leading to the multisystem pathology associated with CF.[7] Progressive loss of lung function is the leading cause of mortality.[8]

The most common disease-causing mutation is *F508del*: approximately 85% of individuals in the US[1] and 80% of individuals in Europe[2] have at least one *F508del* mutation. In the EU, patients with one *F508del* mutation are eligible for treatment with the CFTR modulator ELX/TEZ/IVA (Kaftrio™/Trikafta™). The ELX/TEZ/IVA regimen is the first medicine to demonstrate clinical benefit in patients with a single *F508del* mutation, regardless of the mutation on the second allele. The Phase 3 program in CF subjects 6 years of age and older demonstrated that treatment with ELX/TEZ/IVA results in substantial improvements in lung function, CFTR function, and nutritional status in this population, and was generally safe and well tolerated with a low rate of treatment discontinuation.

The ELX/TEZ/IVA pivotal Phase 3 program demonstrated efficacy in subjects who have at least one *F508del* mutation. However, more than 160 additional *CFTR* mutations have been shown to be responsive to ELX/TEZ/IVA in vitro. CF patients with these mutations do not currently have an indicated CFTR modulator treatment in the EU, nonetheless they are expected to derive clinical benefit from ELX/TEZ/IVA based on (1) current understanding of the biology of the *CFTR* mutations (2) the known mechanism by which CFTR modulators act on defective CFTR proteins that contain these mutations (3) in vitro evidence indicating responsiveness of these proteins to ELX/TEZ/IVA and (4) the established relationship between in vitro responsiveness and clinical benefit.

5.2 Study Rationale

This study will evaluate the efficacy and safety of ELX/TEZ/IVA in patients in the EU who have the more prevalent ELX/TEZ/IVA-responsive non-*F508del CFTR* mutations which are not currently indicated for a CFTR modulator regimen (Section 15).

These mutations are considered ELX/TEZ/IVA-responsive based on either (a) in vitro evidence from the Fischer Rat Thyroid (FRT) cell system, a robust and reproducible in vitro model to measure CFTR-mediated chloride transport[10] or (b) the ability of ELX/TEZ/IVA to increase the activity of the small amounts of functional, full-length CFTR protein produced by non-canonical splice mutations. Extensive clinical data evaluating CF subjects with different *CFTR* mutations indicate that an in vitro FRT response to a CFTR modulator regimen has been predictive of clinical benefits, including improvements in lung functions (as measured by percent predicted forced expiratory volume in 1 second [ppFEV$_1$]), CFTR function (as measured by sweat chloride [SwCl]), and CF-related quality of life (as measured by Cystic Fibrosis Questionnaire – Revised [CFQ-R RD]). The non-canonical splice mutations selected for this study result in low amounts

of functional, full-length CFTR protein, which can be acted upon by CFTR modulators to increase CFTR activity at the cell surface, as demonstrated in a clinical trial of TEZ/IVA and IVA (Study 661-108).

5.3 Risk Assessment

The safety profile of ELX/TEZ/IVA has been adequately characterized, with risks that are readily identified clinically or with routine laboratory monitoring. In previous clinical trials of subjects ≥6 years of age, the rate of adverse events (AEs) leading to treatment discontinuation was low. The most common adverse drug reactions (ADRs) observed on ELX/TEZ/IVA were headache, diarrhea, upper respiratory tract infection, abdominal pain, alanine transaminase (ALT) increased, aspartate transaminase (AST) increased, blood creatine kinase increased, nasal congestion, rash, and rhinorrhea. Serious ADRs that occurred more frequently in the ELX/TEZ/IVA group than in the placebo group were rash events in 3 (1.5%) subjects treated with ELX/TEZ/IVA.

Subjects in this study will continue on their usual standard-of-care CF treatments (e.g., inhaled antibiotics, prednisone, and bronchodilators [Section 9.5]). The overall risk and burden to subjects participating in this study will be minimized as much as possible. Key safety eligibility criteria, close safety monitoring of subjects, prudent stopping rules, and guidance regarding use of concomitant medications have been included in this study protocol.

6 STUDY OBJECTIVES

6.1 Primary Objective

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

6.2 Secondary Objective

To evaluate safety and tolerability of ELX/TEZ/IVA

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) through Week 24

7.2 Secondary Endpoints

- Absolute change from baseline in SwCl through Week 24
- Absolute change from baseline in Cystic Fibrosis Questionnaire- Revised respiratory domain (CFQ-R RD) score through Week 24
- Absolute change from baseline in body mass index (BMI) at Week 24
- Absolute change from baseline in weight at Week 24
- Number of pulmonary exacerbations (PEx) through Week 24
- Safety and tolerability assessments based on AE, clinical laboratory values, ECGs, vital signs, and pulse oximetry

7.3 Other Endpoints

- Absolute change from baseline in BMI z-score (subjects ≤20 years of age) at Week 24
- Absolute change from baseline in weight z-score (subjects ≤20 years of age) at Week 24
- Plasma pharmacokinetic (PK) parameters including ELX, TEZ, IVA, and relevant metabolites

8 STUDY POPULATION

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

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

8.1 Inclusion Criteria

1. Subject (or the subject's legally appointed and authorized representative) will sign and date an informed consent form (ICF) and, when appropriate, an assent form.
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines (as applicable), and other study procedures.
    - For subjects <18 years of age: as judged by the investigator, 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.
3. Subjects (male or female) 6 years of age and older on the date of informed consent.
4. Subjects has an eligible ELX/TEZ/IVA-responsive *CFTR* mutation listed in Table 15-1 and none of the exclusionary mutations in Table 15-2.
5. Subject has stable CF disease, as deemed by the investigator, before randomization.
6. Forced expiratory volume in 1 second (FEV_1) value ≥40% and ≤100% of predicted mean for age, sex, and height (equations of the Global Lung Function Initiative [GLI])[11] at the Screening Visit (spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria[12] for acceptability and repeatability).
7. Subject is able to swallow tablets.

8.2 Exclusion Criteria

1. History of any illness or any clinical condition that might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This may include, but is not limited to:
    - History of allergy, intolerance, or hypersensitivity to any component of the investigational drug product (ELX/TEZ/IVA tablets and IVA tablets) or placebo, including excipients
    - Clinically significant liver cirrhosis with or without portal hypertension
    - Solid organ or hematological transplantation

- Alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator
- Cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years)

2. Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject (as deemed by the investigator).
3. Any of the following abnormal laboratory values at screening:
   - Hemoglobin <10 g/dL
   - Total bilirubin ≥2 × upper limit of normal (ULN)
   - AST, ALT, gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN
   - Abnormal renal function defined as glomerular filtration rate ≤50 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease Study Equation)[13, 14]for subjects ≥18 years of age and ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation)[15] for subjects <18 years of age.
4. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for sinopulmonary 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 *Mycobaterium abscessus*). For subjects who have had a history of a positive culture, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms.
   - The subject has not had a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent, and
   - 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 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.

8. Pregnant and breast-feeding females. Female subjects of childbearing potential (Section 11.5.6.1) must have a negative pregnancy test at the Screening Visit and the Day 1 Visit.
9. Use of restricted medication within specified duration before the first dose of study drug as defined in Table 9-3.
10. Subject, or close relative of the subject, is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site. However, an adult (aged 18 years or older) who is a relative of a study staff member may be enrolled in the study provided that:
    - the adult lives independently of and does not reside with the study staff member, and
    - the adult participates in the study at a site other than the site at which the family member is employed.

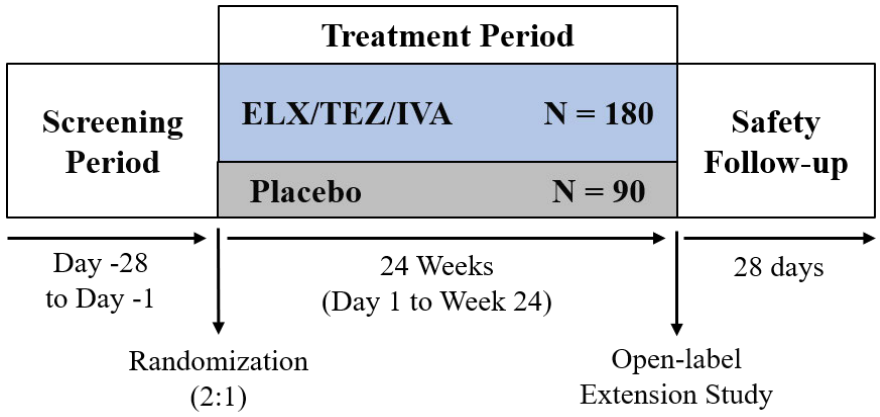
9 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 3 randomized, placebo-controlled, double-blind, parallel group study. Subjects 6 years of age and older with a qualifying non-*F508del,* ELX/TEZ/IVA-responsive *CFTR* mutation listed in Table 15-1 and none of the exclusionary mutations in Table 15-2 may be eligible for enrollment. These qualifying ELX/TEZ/IVA-responsive mutations can be categorized as minimal function (MF)-like and residual function (RF)-like mutations. MF-like mutations have a clinical phenotype without evidence of residual CFTR function. RF-like mutations result in residual CFTR function.

Subjects will be randomized 2:1 (ELX/TEZ/IVA group: placebo group). Randomization will be stratified based on ppFEV$_1$ determined during the Screening Period (<70 versus ≥70), age at the Screening Visit (<18 years old versus ≥18 years old) and *CFTR* genotype (contains ≥1 RF-like mutation versus does not contain an RF-like mutation [as defined in Section 15]).

Figure 9-1 Study VX21-445-124 Design



ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

Approximately 270 subjects will be enrolled in the study with up to approximately 30 subjects per *CFTR* mutation. Up to 10% of subjects may be enrolled with a screening ppFEV$_1$ value >90% and ≤100% (approximately 27 subjects).

The ELX/TEZ/IVA dosing regimen will be based on the subject's age and weight on Day 1 as shown in Table 9-1. Subjects will receive the same dose of ELX/TEZ/IVA throughout the Treatment Period, regardless of change in age or weight.

Table 9-1 Treatment Period Dosages

Treatment Group Subject Age Weight	ELX Dosage	TEZ Dosage	IVA Dosage
ELX/TEZ/IVA			
≥12 years			
All weights	200 mg qd	100 mg qd	150 mg q12h
≥6 to <12 years			
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
<30 kg	100 mg qd	50 mg qd	75 mg q12h
Placebo			
All ages and all weights	0 mg	0 mg	0 mg

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

ELX/TEZ/IVA will be administered as 2 fixed-dose combination (FDC) tablets in the morning and a single IVA monotherapy tablet in the evening (regardless of dosing regimen) as described in Section 9.6.

9.1.1 Screening

Screening Visit assessments are listed in Table 3-1.

Screening will occur within 28 days before administration of study drug. Screening assessments will be used to confirm that subjects meet the eligibility criteria. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent and assent, if applicable from each subject.

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

9.1.1.1 Repetition of Screening Assessment(s)

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

9.1.1.2 Rescreening

Subjects 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.

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)
- 28-day washout period for subjects who have been on an investigational or commercially available CFTR modulator (Table 9-3)

9.1.2 Treatment Period

Treatment Period assessments are listed in Table 3-2.

The Treatment Period will last approximately 24 weeks. Randomization details are provided in Section 9.2 and study drug administration details are provided in Section 9.6.

9.1.3 Follow-up

The Safety Follow-up Visit will occur 28 (± 7) days after the last dose of study drug for subjects who complete study drug dosing and for subjects who prematurely discontinue study drug dosing, as described in Section 9.1.4.

An optional open-label extension safety study will be available for subjects who meet eligibility requirements. The Safety Follow-up Visit is not required for subjects who complete the Week 24 Visit and enroll in the optional open-label extension 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 treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the decision to discontinue study treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (± 7) days after their last dose of study drug. The assessments performed at the Safety Follow-up Visit are listed in Table 3-2.

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

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 3-1 and Table 3-2. Data regarding concomitant antibiotic therapy for sinopulmonary signs/symptoms will also continue to be collected for these subjects.

If a subject withdraws consent or assent for the study, 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; study data and samples collected will remain part of the study (Section 9.10).

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 one of the following:

- For subjects who complete the Treatment Period and enter an open-label extension 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 open-label extension 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 9.1.4)

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 Use of Remote Measures in Extenuating Circumstances

Study visits should be performed in the clinic as specified in Table 3-1 and Table 3-2, 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), Day 1 Visit, and Week 24 Visit 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, Day 1, and Week 24) may be conducted as in-home visits by qualified personnel.
- Study assessments (other than SwCl assessments) may be performed or overseen by qualified personnel conducting the in-home visits.
- Remote monitoring visits may be implemented as applicable (including remote source data verification) and as allowed per local regulations.

9.1.8 Independent Data Monitoring Committee

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

9.2 Method of Assigning Subjects to Treatment Groups

An interactive web or voice response system (IXRS) will be used to assign subjects to treatment. Subjects will be stratified as described in Section 9.1. The randomization code will be produced by Vertex Biostatistics or a qualified randomization vendor. The Vertex study biostatistician will review and approve the production of the final randomization list, which will be reviewed and approved by a designated unblinded biostatistician who is not a member of the Study Execution Team.

9.3 Rationale for Study Elements

9.3.1 Study Design

A randomized, double-blind, controlled study design was selected to evaluate the effects of ELX/TEZ/IVA while avoiding observer bias. Placebo is an appropriate comparator because ELX/TEZ/IVA is not approved for the treatment of CF for the study's patient population in the region(s) where the study will be conducted. A 2:1 (ELX/TEZ/IVA: placebo) randomization ratio will appropriately blind the study, while also providing adequate power for a between-group analysis of efficacy in this rare patient population.

This study will have a 24-week treatment duration to allow for the collection of data for outcomes that require longer treatment durations to demonstrate an effect (e.g., changes in nutritional status and rates of PEx).

9.3.2 Study Population

The study population will include subjects with non-*F508del* ELX/TEZ/IVA-responsive *CFTR* mutations that are more prevalent in the EU but are not currently indicated for a CFTR modulator regimen (Section 15).These mutations are considered ELX/TEZ/IVA-responsive based on either (a) in vitro (FRT cell) evidence from the FRT cell system, a robust and reproducible in vitro model to measure CFTR-mediated chloride transport or (b) the ability of ELX/TEZ/IVA to increase the activity of the small amounts of normal, full-length CFTR protein produced by non-canonical splice mutations (Section 5.2).

9.3.3 Study Drug Dose

The ELX/TEZ/IVA dosing will be based on the posology for patients with at least one *F508del* mutation, which is based on the subject's age and weight as shown in Table 9-2. Subjects will receive the same dose of ELX/TEZ/IVA throughout the Treatment Period, regardless of change in age or weight.

Table 9-2 ELX/TEZ/IVA Dosing

Treatment Group Subject Age Subject Weight	ELX/TEZ/IVA (Morning Dose = 2 tablets)	IVA (Evening Dose = 1 tablet)
ELX/TEZ/IVA		
≥12 years		
All weights	ELX 100 mg/TEZ 50 mg/IVA 75 mg	IVA 150 mg
≥6 to <12 years		
≥30 kg	ELX 100 mg/TEZ 50 mg/IVA 75 mg	IVA 150 mg
<30 kg	ELX 50 mg/TEZ 25 mg/IVA 37.5 mg	IVA 75 mg
Placebo		
All ages and weights	ELX 0 mg/TEZ 0 mg/IVA 0 mg	IVA 0 mg

ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor
Note: Weight is based on subject's weight on Day 1.

9.3.4 Rationale for Study Assessments

The safety, pharmacokinetic (PK), efficacy, and PD assessments are standard parameters for clinical studies in drug development and are generally recognized as reliable, accurate, and relevant to the study of CF subjects. A number of these assessments are part of routine clinical care for pediatric CF patients; however, they may be performed more frequently as part of this study than they would as routine care. 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.

9.4 Study Restrictions

Study restrictions are summarized in Table 9-3.

Table 9-3 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	

Table 9-3 Prohibited Medications

Medication	Timing of Restriction		Rationale
	Start of Restriction	End of Restriction	
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 randomized, details of prior medication will be documented only in the subjects' source documents.

- Subjects should remain on a stable treatment regimen for their CF from 28 days before the Day 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 spirometry assessments performed according to the guidelines provided in Section 11.4.1.

9.6 Administration

Study drug should be administered with a fat-containing meal or snack, such as a standard "CF" meal or snack or a standard meal according to the following guidelines:

1. It is recommended that the dose be taken within approximately 30 minutes of the start of the meal or snack.
2. All doses of study drug (morning and evening, as applicable) should be administered at approximately every 12 hours (± 2 hours) on each dosing occasion (e.g., if the morning doses of study drug are administered at 08:00 hour on Day 1, all subsequent morning doses should be administered between 06:00 hour and 10:00 hour).
3. On days of scheduled visits, the morning dose of study drug will be administered under the supervision of site medical staff or a home health nurse after predose assessments have been completed. The meal or snack will be provided by the site on in-clinic visit days for the morning dose of study drug.
4. For visits after the Day 1 Visit, subjects will be instructed to return all used and unused study drug to the site or the home health nurse; study drug will be dispensed at each visit, as appropriate.
5. 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.

9.7 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.

9.8 Dose Modification for Toxicity

Modifications of the study drug dose are prohibited. Should any unacceptable toxicity arise, individual subjects will be withdrawn from the study and dosing will cease (Section 9.1.4).

9.9 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.

9.9.1 Liver Function Tests

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

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

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

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

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

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

Study drug administration **must be discontinued** if the following criterion is met:

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

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

If an alternative, reversible cause of transaminase elevation (with or without increased bilirubin or clinical jaundice) has been identified, subjects may receive study drug 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.

9.9.2 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; Section 13.1.2.1). The investigator will notify the medical monitor of any rash that results in interruption of study drug, is Grade 3 or higher, or is an SAE. Investigators should consider additional evaluation including laboratory testing (e.g., complete blood count with differential, liver function tests), photographs of the rash, and dermatology consultation. The investigator may consider resumption of study drug if considered clinically appropriate.

9.10 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 from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. A subject who withdraws from study drug treatment will continue to be followed unless the subject withdraws consent.

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

- Meets any of the stopping (discontinuation) criteria (Section 9.9)
- Becomes pregnant (Section 11.5.6.2)

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit, if applicable (see Section 9.1.3), 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.

9.11 Replacement of Subjects

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

10 STUDY DRUG INFORMATION AND MANAGEMENT

Study drug refers to ELX/TEZ/IVA, IVA and their matching placebos.

10.1 Preparation and Dispensing

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

10.2 Packaging and Labeling

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

10.3 Study Drug Supply, Storage, and Handling

ELX/TEZ/IVA will be supplied as FDC film-coated tablets containing at the strengths shown in Table 10-1. Matching ELX/TEZ/IVA placebo tablets will be of similar size and appearance and contain 0 mg ELX, 0 mg TEZ, and 0 mg IVA.

IVA will be supplied as tablets at strengths shown in Table 10-1. Matching IVA placebo tablets will be of similar size and appearance and contain 0 mg IVA.

Table 10-1 Study Drug

Drug Name, Dosing Form, Route	Tablet Strengths	
ELX/TEZ/IVA, FDC tablet, oral		
ELX	100 mg	50 mg
TEZ	50 mg	25 mg
IVA	75 mg	37.5 mg
ELX/TEZ/IVA-matching placebo, tablet oral	0/0/0 mg	0/0/0 mg
IVA, tablet, oral	150 mg	75 mg
IVA-matching placebo, tablet oral	0 mg	0 mg

ELX: elexacaftor; FDC: fixed-dose combination; IVA: ivacaftor; TEZ: tezacaftor
Note: See Section 9.6 for details on study drug administration.

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

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 they are 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 (in-clinic and telephone contact), site personnel will review that the subject is compliant with study drug dosing and remind the subject of study drug dosing requirements.

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

10.7 Blinding and Unblinding

This is a double-blind study.

10.7.1 Blinding

All subjects (and their parents/caregivers/companions) and study personnel will be blinded to subject treatment assignments except for the following individuals:

- Any site personnel for whom this information is important to ensure the safety of a subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of a subject and a fetus in the event of a pregnancy
- The unblinded site monitor and unblinded trip report reviewer

- An unblinded pharmacist at the contract research organization (CRO) for dispensing study drug
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations
- External vendor (unblinded) statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IXRS Management for IXRS oversight and system administration
- Vertex Clinical Supply Chain
- The bioanalytical CRO laboratory/vendor personnel managed by Vertex Bioanalysis
- The Vertex bioanalytical personnel responsible for reviewing raw data from the bioanalytical CRO, who is not a member of the Study Team (the Vertex bioanalytical Study Team member will continue to be blinded)

Vertex medical monitor may, for matters relating to safety, unblind individual subjects at any time.

Access to Spirometry and SwCl Results:

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

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

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

10.7.2 Unblinding

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

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

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

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

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

11 ASSESSMENTS

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

11.1 Subject and Disease Characteristics

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

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

11.2 Pharmacokinetics

11.2.1 Blood Sampling

Blood samples will be collected as shown in Table 3-2 to determine plasma concentrations of ELX, TEZ, IVA and their relevant metabolites. Blood samples will be collected within 60 minutes before the morning dose of ELX/TEZ/IVA. To reduce subject burden and minimize discomfort of blood draws, a topical or local anesthetic may be used at the discretion of the investigator. Site personnel may only make a maximum of 3 attempts to draw blood at any single visit.

These samples may also be used for further evaluation of the bioanalytical method, or for exploratory analyses that provide information on the metabolic pathways used by or affected by ELX, which may not be included in the CSR.

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

Plasma concentration samples collected from subjects treated with placebo will not be routinely analyzed.

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 and the PK Sample Handling Guidelines.

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.

11.3 Exploratory Assessments

Blood samples will also be collected from subjects who weigh ≥22 kg at the screening visit for potential exploratory evaluation of changes in ribonucleic acid (RNA) and protein markers (serum and plasma) following treatment with ELX/TEZ/IVA, or evaluation of associations between RNA or protein markers with PK, PD, treatment response, and AEs. To reduce subject burden and minimize discomfort of blood draws, a topical or local anesthetic may be used at the discretion of the investigator. Site personnel may only make a maximum of 3 attempts to draw blood at any single visit.

These data will be used for internal exploratory purposes. Detailed procedures for the collection of blood samples and additional procedures for processing and handling samples will be provided in a separate document.

11.4 Efficacy

11.4.1 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines[12] and according to the additional guidelines that follow.

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

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

During the Screening Period, spirometry assessments may be performed pre- or post-bronchodilator. At all other visits, all spirometry assessments should be performed pre-bronchodilator. During the Treatment Period, spirometry assessments must be performed before study drug dosing (Section 9.6) at approximately the same time at each visit. In the event that a subject forgets to withhold bronchodilator(s), spirometry should be performed according to the following:

- If a subject's Day 1 spirometry assessment is pre-bronchodilator, but, on a subsequent visit, the subject forgets to withhold bronchodilator use, a post-bronchodilator spirometry assessment will be obtained for that visit only, and the visit will not be rescheduled.

- If, on Day 1, the subject forgets to withhold his/her dose of bronchodilator, spirometry should be performed post-bronchodilator, and all subsequent spirometric measurements (according to the schedule of assessments) should be performed post-bronchodilator.
- Each spirometry assessment will be recorded in the source documents as pre- or post-bronchodilator.

Spirometers will be provided to be used for all study assessments. During study visits, spirometry assessments will be conducted per Table 3-1 and Table 3-2 and will be performed on more than one spirometer as applicable. All spirometry data will be transmitted to a centralized spirometry service for quality review. The investigator's assessment of the spirometry results will be used for the screening assessment and determination of eligibility.

See Section 10.7.1 for information about access to spirometry results.

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

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

11.4.2 Sweat Chloride

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

See Section 10.7.1 about access to SwCl results.

11.4.3 Cystic Fibrosis Questionnaire – Revised

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

Subjects/caregivers will be asked to complete the CFQ-R in their native language, if validated translations are available.[16, 17] If there is no validated translation available in the subject's native language, the subject will not complete the questionnaire. Copies of the CFQ-R used will be provided in the Study Reference Manual. Validated translations of the CFQ-R, if available, will be provided for participating centers in non-English-speaking countries.[18, 19] The version and format of CFQ-R will be based on age at informed consent, regardless of whether the subject changes age during the study.

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

11.4.4 Height and Weight

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

For subjects whose date of informed consent occurs after their 21st birthday, height will not be collected in this study. For subjects whose date of informed consent occurs on or before their 21st birthday, height will be collected through the first visit after the subject's 21st birthday and does not need to be collected at future visits

11.4.5 Other Events Related to Outcome

11.4.5.1 Antibiotic Therapy for Sinopulmonary Sign/Symptoms

New or changed antibiotic therapy (intravenous [IV], inhaled, or oral) for the following sinopulmonary signs/symptoms will be determined and documented at visits as indicated in Table 3-1 and Table 3-2:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature above 38°C (equivalent to approximately 100.4°F)
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination (PE) of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

For this study, PEx is defined as a new or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the above signs/symptoms. This definition is based on the definition of a PEx used in previous clinical studies, including IVA clinical studies.[20, 21]

It is recommended that the study drug not be interrupted during a PEx unless, in the opinion of the investigator, it would be in the best interest of the subject.

11.4.5.2 Hospitalization for CF

Subjects will be queried about planned and unplanned hospitalizations lasting ≥24 hours that occurred during the study. The dates of hospitalizations and the reasons for hospitalizations will be documented.

For any hospitalization (planned and unplanned), the procedures for safety reporting should also be followed.

11.5 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, and PEs. Safety will be monitored continuously from the signing of the ICF through completion of study participation (defined in Section 9.1.6) according to the schedule of assessments (Table 3-1 and Table 3-2).

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.

11.5.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory, with the exception of urine pregnancy tests. As described below, urine pregnancy tests will either be analyzed by the site or at home using a home pregnancy test kit.

On Day 1, blood samples will be collected before the first dose of the study drug. At all other scheduled visits, these samples will be collected at any time during the visit. To reduce subject burden and minimize discomfort of blood draws, local anesthetic may be used at the discretion of the investigator. Site personnel may only make a maximum of 3 attempts to draw blood.

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

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

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis[a]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen[b]	Erythrocytes	Nitrite
Creatinine	Mean corpuscular volume	Urobilinogen
Sodium	Platelets	Urine protein
Potassium	Reticulocytes	pH
Calcium	Leukocytes	Urine blood
Chloride	Differential (absolute and percent):	Specific gravity
Magnesium	Eosinophils	Urine ketones
Bicarbonate	Basophils	Urine bilirubin
Phosphate	Neutrophils	Urine glucose
Total bilirubin, direct bilirubin	Lymphocytes	
Alkaline phosphatase	Monocytes	
Aspartate transaminase	**Coagulation**	
Alanine transaminase	Activated partial thromboplastin time	
Amylase	Prothrombin time	
Lipase	Prothrombin time International Normalized Ratio	
Gamma-glutamyl transferase		
Protein		
Albumin		
Creatine kinase		
Thyroid-stimulating hormone		
Urate		
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.

Additional Tests at Screening: The following additional tests will be performed during screening to assess eligibility:

- Beta-human chorionic gonadotropin (β-hCG) for all female subjects ≥9 years of age and for all female subjects who have undergone menarche.
- Serum follicle-stimulating hormone (FSH) for suspected postmenopausal female subjects only. Levels will be within the laboratories range for postmenopausal for subjects to be considered of non-childbearing potential.

Pregnancy Testing: All female subjects who are ≥9 years of age and all female subjects who have undergone menarche (regardless of age) will have a serum pregnancy test at the Screening Visit. Females of childbearing potential (as defined in Section 11.5.6.1) will also have pregnancy tests at in-clinic visits and at-home urine pregnancy tests as shown in Table 3-2.

Serum pregnancy tests will be performed by site medical staff and analyzed at the central laboratory. Urine pregnancy tests will either be performed and analyzed at the site or at home using a home kit provided by the site. Results will be reported to the site by telephone or telemedicine contact.

The urine pregnancy test on Day 1 must be negative before the first dose of study drug is administered to the subject. Additional pregnancy tests may be required according to local regulations and/or requirements.

FSH (Screening Period only): Blood samples for FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea (Section 11.5.6.1). Serum FSH levels must be in the postmenopausal range as determined by the laboratory performing the test.

CFTR genotyping (Screening Period only): *CFTR* genotyping will be performed for all subjects. A subject's screening *CFTR* genotype **must** confirm eligibility before the subject is randomized. Specific instructions will be provided in the Laboratory Manual.

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

For purposes of study conduct, 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, Vital Signs, and Pulse Oximetry

A full 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.

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.

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

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 the Safety Follow-up Visit 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 QT interval corrected by Fridericia's formula (QTcF) is increased by >60 msec from the baseline or an absolute QTcF value is ≥500 msec for any scheduled ECG, 2 additional ECGs will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>60 msec from baseline or ≥500 msec), a single ECG will be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. A subject with a QTcF value above the threshold value will discontinue dosing.

11.5.5 Ophthalmological Examinations (Subjects <18 Years of Age)

Ophthalmologic examinations will be conducted only for subjects who are <18 years of age on the date of initial consent. The examination does not need to be completed if there is documentation of bilateral lens removal for the subject.

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

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

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.

In addition to the screening ophthalmologic examination, a single follow-up ophthalmologic examination will be conducted for all subjects who were <18 years of age on the date of initial consent and who completed at least 12 weeks of study drug treatment. 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 3-2.

Any clinically significant abnormal findings will be reported as AEs.

11.5.6 Contraception and Pregnancy

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

11.5.6.1 Contraception

Contraception requirement for a couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. True abstinence must be practiced from the Screening Visit through 90 days after the last dose of study drug.
- If the male is infertile (e.g., bilateral orchiectomy). If a male subject is assumed to have complete bilateral absence of the vas deferens, infertility must be documented before the first dose of study drug (e.g., examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound).
- Same-sex relationships
- If the female is of non-childbearing potential. For a subject to be considered of non-childbearing potential, the female must meet at least 1 of the following criteria:
    - Less than 9 years of age and has not achieved menarche
    - Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum FSH level within the laboratory's reference range for postmenopausal females
    - Documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy

  Note: All other females (including females <9 years of age who have achieved menarche and females with tubal ligations) will be considered to be of childbearing potential.

For subjects for whom the contraception requirement is not waived, study participation requires a commitment from the subject that at least 1 acceptable method of contraception is used as a couple. Methods of contraception must be in successful use from signing of consent approximately 28 days before the first dose of study drug (unless otherwise noted), and until 90 days following the last dose of study drug. Additional contraception requirements may need to be followed according to local regulations and/or requirements. Acceptable methods of contraception are listed in Table 11-2.

Table 11-2 Acceptable Methods of Contraception (Applies to Subjects For Whom Contraception Requirements Are Not Waived)

	Male Subjects and Their Female (Non-study) Partners	Female Subjects and Their Male (Non-study) Partners
Vasectomy performed at least 6 months previously, with a documented negative postvasectomy semen analysis for sperm	Yes	Yes
Bilateral tubal occlusion (e.g., ligation) performed at least 6 months previously	Yes	Yes
Male or female condom with or without spermicide[a]	Yes	Yes
Female barrier contraception (such as diaphragm, cervical cap, or sponge) with spermicide	Yes	Yes
Continuous use of an intrauterine device for at least 90 days before the first dose of study drug	Yes	Yes

Table 11-2 Acceptable Methods of Contraception (Applies to Subjects For Whom Contraception Requirements Are Not Waived)

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

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

Additional notes:

- If over the course of the study the subject meets the criteria for waiving the contraception requirements, the subject does not need to follow the contraceptive methods listed in Table 11-2.
- Male subjects must not donate sperm during the period starting from the first dose of study drug until 90 days after the last dose of study drug.
- Female subjects should not nurse a child during the period starting from the first dose of study drug until 90 days after the last dose of study drug.
- For male subjects with a female partner of childbearing potential, the couple should not plan to become pregnant during the study or within 90 days after the last dose of study drug, with the exception of couples who plan to become pregnant by artificial insemination using sperm banked by the male subject before the first dose of study drug or sperm from another source.

11.5.6.2 Pregnancy

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

If a female subject becomes pregnant while participating in the study, the study drug will be permanently discontinued immediately. The investigator will 1) notify the medical monitor and Vertex GPS within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy, and 2) send the Pregnancy Information Collection Form to Vertex GPS. Male subjects with female partners who become pregnant during the study must use a male condom to avoid exposure of a potential embryo or fetus to study drug via the seminal fluid.

The subject or partner will be followed until the end of the pregnancy only if on blinded treatment, or if they have been unblinded and have received active drug. The infant will be followed for 1 year after birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself is not an AE.

12 STATISTICAL ANALYSIS

12.1 Sample Size and Power

Approximately 270 subjects will be enrolled and randomized (2:1) to the ELX/TEZ/IVA arm or the placebo arm.

The primary endpoint is the absolute change from baseline in $ppFEV_1$ through Week 24. The primary null hypothesis to be tested is that the mean absolute change from baseline in $ppFEV_1$ through Week 24 is the same for the ELX/TEZ/IVA and placebo treatment groups. The null hypothesis will be tested at a 2-sided significance level of 0.05.

Assuming a within-group SD of 9 percentage points and a 10% dropout rate at Week 24, a total sample size of 270 subjects (180 subjects in the ELX/TEZ/IVA group and 90 subjects in placebo group) will have approximately 90% power to detect a difference of 4.0 percentage points for the mean absolute change from baseline in $ppFEV_1$ through Week 24 between the 2 treatment groups, based on a 2-sided 2-sample *t*-test at a significance level of 0.05.

12.2 Analysis Sets

The following analysis sets are defined: All Subjects Set, Full Analysis Set (FAS), and Safety Set.

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

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

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

12.3 Statistical Analysis

This section presents a summary of the principal features of the planned statistical 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.

12.3.1 General Considerations

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, median, minimum value (min), and maximum value (max).

Categorical variables will be summarized using counts and percentages.

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 the SAP.

Absolute change from baseline will be calculated as Post-baseline value − Baseline value.

The **Treatment-emergent (TE) Period** will include the time from the first dose of study drug to 28 days after the last dose of study drug or to the completion of study participation (as defined in Section 9.1.6), whichever occurs first.

12.3.2 Background Characteristics

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, exposure, compliance, and important protocol deviations will be summarized.

Details of the analysis will be provided in the SAP.

12.3.3 Efficacy and Pharmacodynamics Analysis

12.3.3.1 Analysis of Primary Efficacy Endpoint

The primary endpoint is the absolute change from baseline in $ppFEV_1$ through Week 24.

The primary analysis will be based on a mixed-effects model for repeated measures (MMRM). The model will include the absolute change from baseline in $ppFEV_1$ at Day 15, Week 4, Week 8, Week 16, and Week 24 as the dependent variable; treatment group, visit, and treatment-by-visit as fixed effects; additional covariates will be included as appropriate and details will be specified in the SAP. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the *F* test for fixed effects will be estimated using the Kenward-Roger approximation. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, a compound symmetry covariance structure will be used instead. Conditional on the observed data and covariates, missing data will be assumed to be missing at random; consequently, no imputation of missing data will be performed.

The primary result obtained from the model will be the estimated treatment difference through Week 24. The adjusted mean with a 2-sided 95% CI and a 2-sided *P* value will be provided.

Furthermore, the adjusted mean and treatment difference at each post-baseline visit will also be provided, obtained from the model.

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

Supportive analyses and subgroup analyses of the primary efficacy variable will also be described in the SAP.

12.3.3.2 Analysis of Secondary Efficacy Endpoints

The secondary efficacy variables include:

- **Absolute change from baseline in SwCl through Week 24**: Analysis of this PD variable will be based on an MMRM model similar to the analysis of the primary efficacy variable. Data obtained from Day 15, Week 4, Week 8, Week 16, and Week 24 Visits will be included in the model.
- **Absolute change from baseline in the CFQ-R RD score through Week 24:** Analysis of this domain will be based on an MMRM model similar to the analysis of the primary efficacy variable. Data obtained from Week 4, Week 8, Week 16, and Week 24 Visits will be included in the model.

- **Absolute change from baseline in BMI at Week 24:** Analysis of this variable will be based on an MMRM model similar to the analysis of the primary efficacy variables. Data obtained from Day 15, Week 4, Week 8, Week 16, and Week 24 Visits will be included in the model.
- **Absolute change from baseline in weight at Week 24:** Analysis of this variable will be based on an MMRM model similar to the analysis of the primary efficacy variables. Data obtained from Day 15, Week 4, Week 8, Week 16, and Week 24 Visits will be included in the model.
- **Number of PEx through Week 24:** Analysis of this variable will be performed using a negative binomial regression model with a fixed effect for treatment, as well as additional covariates as appropriate (details will be specified in the SAP). The logarithm of the subject specific PEx analysis period duration (defined in the SAP) will be treated as the offset in the model.

12.3.3.3 Analysis of Other Efficacy Endpoints

The other efficacy variables include absolute change from baseline in BMI z-score at Week 24 and absolute change from baseline in weight z-score at Week 24. The analysis details for these variables will be described in the SAP.

12.3.3.4 Multiplicity Adjustment

A hierarchical testing procedure will be used to control the overall type I error at an alpha of 0.05. The secondary endpoints described in Section 12.3.3.2 will be formally tested at an alpha of 0.05 only if the primary analysis of absolute change from baseline in ppFEV$_1$ through Week 24 is statistically significant. For a test at any step to be considered statistically significant within the testing hierarchy, it must be statistically significant, and all previous tests (if any) within the hierarchy must be statistically significant at the 0.05 level 2-sided. Additional details will be provided in the SAP.

12.3.3.5 Missing Data Handling

Details of the handling of missing data for the primary and secondary endpoints will be described in the SAP.

12.3.4 Safety Analysis

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

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

For safety analyses, no statistical hypothesis testing will be conducted. Additional details will be provided in the SAP.

12.4 Interim Analysis

Not applicable.

12.5 Independent Data Monitoring Committee Analysis

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

12.6 Clinical Pharmacology Analysis

12.6.1 Pharmacokinetic Analysis

The PK of ELX, TEZ, IVA and their relevant metabolites will be described using summary statistics. Preliminary review and analyses of the drug concentrations may be done before database lock under the conditions of masked identifications of the subject concentrations.

Details of the analyses will be in the CPAP.

12.6.2 Pharmacodynamic Analysis

12.6.3 Pharmacokinetic/Pharmacodynamic Analyses

A population PK analysis of plasma concentration versus time data of ELX/TEZ/IVA may be performed using the nonlinear mixed-effects modeling approach. A more detailed description of the methodology to be followed will be in either the CPAP or the population PK/PD analysis plan. Listings of ELX, TEZ, and IVA and relevant metabolite plasma concentration data will be in the bioanalytical report. The population PK analysis will be in a stand-alone document.

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 in source documents from the time the ICF is signed until completion of study participation (Section 9.1.6)

All subjects, or their 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 source documents. AEs for subjects who are screened but not subsequently enrolled will be recorded only in the subject's source documents. The following data will be documented for each AE:

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

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed July 2021). 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 July 2021)
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).

AE: adverse event

13.1.1.6 Study Drug Action Taken

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

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

Classification[a]	Definition
Dose not changed	Study drug dose not changed in response to an AE
Dose reduced	Study drug dose reduced in response to an AE

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

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

AE: adverse event

[a] Refer to Sections 9.7 and 9.9 for directions regarding what drug actions are permitted per protocol.

13.1.1.7 Adverse Event Outcome

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

Table 13-4 Classifications for Outcome of an AE

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

AE: adverse event

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

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

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation and is suspected of being a delayed toxicity due to administration of the study drug)
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred
- Inpatient hospitalization or prolongation of hospitalization

- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Congenital anomaly or birth defect
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home)

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

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

13.1.2.2 Reporting and Documentation of Serious Adverse Events

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

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

Please send completed SAE Forms to Vertex GPS via:

Email: globalpatientsafety@vrtx.com (preferred choice)

Fax: +1-617-341-6159

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

SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be recorded on the Vertex Clinical Trial Safety Information Collection Form (hereafter referred to as the "SAE Form") using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for relationship to the investigational study drug(s) and possible etiologies. On the SAE Form, relationship to study drug(s) will be assessed

only as related (includes possibly related) or not related (includes unlikely related), and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report the outcome to Vertex using the SAE Form.

13.1.2.3 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities, 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, if allowed by local regulations.

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, 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 data, 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 regulatory authorities, including the IRB/IEC, may also request access to all study records, including source documentation, for inspection.

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. The investigator will affirm the completeness and accuracy of the data by signing each casebook before data lock. If applicable, periodic investigator signatures may also be required.

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

The study will be monitored by Vertex or its designee in accordance with written procedures. Monitoring and auditing procedures developed or approved by Vertex for these activities comply with GCP regulatory requirements and guidelines.

The monitoring strategy may include onsite, remote, and central monitoring activities, in accordance with local regulations. The study site monitor will ensure that the study is conducted according to the protocol design and regulatory requirements.

13.5 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 will be placed in the investigator's study file.

13.6 Confidentiality and Disclosure

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

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

13.7 Publications and Clinical Study Report

13.7.1 Publication of Study Results

Vertex is committed to reporting the design and results of all clinical studies in a complete, accurate, balanced, transparent, and timely manner, consistent with Good Publication Practices (GPP3).[22]

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

Authorship: Authorship of publications will be determined based on the Recommendations for Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states that authorship should be based on the following 4 criteria[23]:

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2. Drafting of the article or revising it critically for important intellectual content;

3. Final approval of the version to be published; and
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

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

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

13.7.2 Clinical Study Report

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

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15 APPENDIX A: ELIGIBLE *CFTR* GENOTYPES

To be eligible for enrollment, subjects must meet both of the following criteria:

- At least 1 ELX/TEZ/IVA-responsive mutation listed in Table 15-1. Sections 5.2 and 9.3.2 describe the rationale for why these mutations are considered to be responsive to ELX/TEZ/IVA.
- None of the exclusionary mutations listed in Table 15-2. Subjects with these mutations are eligible for treatment with a commercial approved CFTR modulator; subjects with *F508del* are eligible for treatment with ELX/TEZ/IVA (Kaftrio™/Trikafta™) and subjects with the remaining mutations are eligible for treatment with IVA (Kalydeco™).

A subject who has 1 eligible mutation and 1 exclusionary mutation will not be eligible for enrollment in the study.

Table 15-1 Eligible ELX/TEZ/IVA-responsive *CFTR* mutations

RF-like mutations			MF-like mutations
2789+5G>A	*L206W*	*S945L*	*G85E*
3272-26A>G	*V232D*	*L997F*	*R347P*
3849+10kbC>T	*T338I*	*R1066H*	*L1077P*
P5L	*R347H*	*D1152H*	*M1101K*
R117C	*A455E*		

Note: A subject must have at least 1 of the mutations listed above to be eligible for the study.

Table 15-2 Exclusionary *CFTR* mutations

F508del	*S549N*	*G551S*	*S1255P*
R117H	*S549R*	*G1244E*	*G1349D*
G178R	*G551D*	*S1251N*	

Note: If a subject has any of the mutations listed above, they will not be eligible for the study.

Maximum Enrollment Per Mutation

Enrollment for each *CFTR* mutation listed in Table 15-1 will be capped at approximately 30 subjects.

If a subject has 2 eligible *CFTR* mutations, the subject may be screened if at least 1 of their 2 eligible mutations has less than approximately 30 subjects enrolled at the time of screening.

16 APPENDIX B: BLOOD SAMPLE VOLUMES BY VISIT

Blood sample volumes to be drawn at each visit are presented in Table 16-1.

Table 16-1 Blood Sample Volumes by Visit (mL)

	Study Visit											
Subject weight	**Screening**	**Day 1**	**Day 15**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**ETT**	**SFU**	**Total[a]**
≥22 kg	10.0	17.5	6.0	8.0	6.0	0	13.5	0	10.0	8.0	8.0	79.0
<22 kg	10.0	10.0	6.0	8.0	6.0	0	6.0	0	10.0	8.0	8.0	64.0

ETT: Early Termination of Treatment; SFU: Safety Follow-up

[a] Total does not include sample volumes from the ETT Visit

17 PROTOCOL SIGNATURE PAGES

17.1 Sponsor Signature Page

Protocol #: VX21-445-124	Version #: 3.0	Version Date: 21 April 2022
Study Title: A Phase 3 Double-blind, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of ELX/TEZ/IVA in Cystic Fibrosis Subjects 6 Years of Age and Older With a Non-*F508del* ELX/TEZ/IVA-responsive *CFTR* Mutation		

17.2 Investigator Signature Page

Protocol #: VX21-445-124	Version #: 3.0	Version Date: 21 April 2022
Study Title: A Phase 3 Double-blind, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of ELX/TEZ/IVA in Cystic Fibrosis Subjects 6 Years of Age and Older With a Non-*F508del* ELX/TEZ/IVA-responsive *CFTR* Mutation		

I have read Protocol VX21-445-124, Version 3.0, and agree to conduct the study according to its terms. I understand that all information concerning ELX/TEZ/IVA and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date