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VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3b, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 6 Through 11 Years of Age Who Are Heterozygous for the *F508del* Mutation and a Minimal Function Mutation (F/MF)

Vertex Study Number: VX19-445-116

EudraCT Number: 2019-003554-86

Date of Protocol: 18 December 2019 (Version 1.0)

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2 PROTOCOL SYNOPSIS

Title A Phase 3b, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 6 Through 11 Years of Age Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)

Brief Title A Study Evaluating Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Subjects 6 through 11 Years of Age With Cystic Fibrosis and F/MF genotypes

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

Objectives

Primary Objective

To evaluate the efficacy of elexacaftor (VX-445; ELX)/tezacaftor (TEZ)/ivacaftor (IVA) in subjects 6 through 11 years of age with cystic fibrosis (CF), heterozygous for *F508del* and a minimal function (MF) mutation (F/MF)

Secondary Objective

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

Endpoints

Primary Endpoint

Absolute change in lung clearance index$_{2.5}$ (LCI$_{2.5}$) from baseline through Week 24

Secondary Endpoints

- Absolute change in sweat chloride (SwCl) from baseline through Week 24
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, standard 12-lead electrocardiograms (ECGs), vital signs, pulse oximetry

[redacted]

Number of Subjects Approximately 108 subjects will be randomized (1:1) to the ELX/TEZ/IVA group or the placebo group.

Study Population Male and female subjects 6 through 11 years of age with CF who have F/MF genotypes.

Investigational Drug

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

Activity: CFTR corrector, CFTR corrector, and CFTR potentiator

Strength and route of administration:

- 50-mg ELX/25-mg TEZ/37.5-mg IVA fixed-dose combination (FDC) tablets

for oral administration

- 100-mg ELX/50-mg TEZ/75-mg IVA FDC tablets for oral administration

Active substance: IVA (VX-770)

Activity: CFTR potentiator

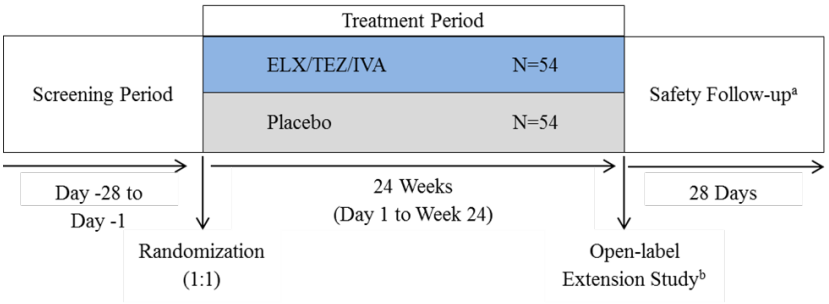
Strength and route of administration:

- 75-mg IVA tablet for oral administration
- 150-mg IVA tablet for oral administration

Study Duration Excluding the Screening Period, the total study duration is approximately 28 weeks (24 weeks for the Treatment Period, and 4 weeks for the Safety Follow-up Period).

Study Design This is a Phase 3b, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in CF subjects 6 through 11 years of age with F/MF genotypes.

Figure 2-1 VX19-445-116 Study Design



ELX: elexacaftor; IVA: ivacaftor; N: number of subjects; TEZ: tezacaftor

Note: Subjects will be randomized 1:1 to receive ELX/TEZ/IVA or placebo

[a] The Safety Follow-up Visit is scheduled to occur 28 days (± 7 days) after the last dose.

[b] Subjects who complete the visits in the Treatment Period, regardless of whether they are on a treatment interruption, will be offered the opportunity to enroll in an optional open-label extension safety study evaluating ELX/TEZ/IVA. The Safety Follow-up Visit is not required for subjects who complete the Week 24 Visit and have enrolled in an open-label study within 28 days after the last dose of study drug.

Subjects will receive ELX/TEZ/IVA or placebo at the doses in Table 2-1 based on their weight at the Screening Visit.

Table 2-1 Treatment Period Groups and Dosages

Treatment Group Weight at Screening Visit	**ELX Dosage**	**TEZ Dosage**	**IVA Dosage**
ELX/TEZ/IVA			
<30 kg	100 mg qd	50 mg qd	75 mg q12h
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
Placebo	0 mg	0 mg	0 mg

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

Randomization will be stratified by $LCI_{2.5}$ determined at the Screening Visit (<10 versus ≥10) and weight at the Screening Visit (<30 kg versus ≥30 kg).

Assessments	**Efficacy Assessments:** Multiple-breath washout (MBW), [redacted] **PD Assessment:** Sweat chloride **Safety Assessments:** AEs, clinical laboratory assessments, ECGs, vital signs, pulse oximetry, physical examinations, and ophthalmologic examinations
[redacted]	
Statistical Analyses	The primary efficacy endpoint is the absolute change in $LCI_{2.5}$ from baseline through Week 24. The primary null hypothesis to be tested is that the mean absolute change in $LCI_{2.5}$ from baseline through Week 24 is the same for the 2 treatment groups, ELX/TEZ/IVA and placebo. The null hypothesis will be tested at a 2-sided significance level of 0.05. Assuming a within-group standard deviation (SD) of 1.5 and a 10% dropout rate through Week 24, a sample size of 54 subjects in each treatment group (108 subjects total) will have approximately 90% power to detect a difference of -1.0 for the mean absolute change in $LCI_{2.5}$ from baseline through Week 24 between the 2 treatment groups, based on a 2-sided 2-sample t-test at a significant level of 0.05. The analysis of the primary efficacy endpoint, absolute change in $LCI_{2.5}$, will be based on a mixed-effects model for repeated measures (MMRM). The primary result obtained from the model will be the estimated treatment difference through Week 24, with a 2-sided 95% CI and a 2-sided *P* value provided. The treatment difference at each post-baseline visit will also be estimated and provided. The safety endpoints include treatment-emergent AEs, clinical laboratory values, ECGs, vital signs, pulse oximetry. The safety analysis will be descriptive only.
DMC Reviews	A data monitoring committee (DMC) will conduct periodic safety review(s) of study data as outlined in the DMC charter.

3 SCHEDULE OF ASSESSMENTS

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

All visits are to be scheduled relative to the Day 1 visit (first dose of randomized study drug). For example, the Week 4 (± 5 days) Visit would occur after 4 weeks of study drug administration has been completed.

Table 3-1 Study VX19-445-116: Screening

Event/Assessment	Screening Visit Day -28 to Day -1	Comments
Informed consent (and assent, if applicable)	X	
Demographics	X	Section 11.1
Medical history	X	Section 11.1
Height and weight	X	Measured with shoes off.
Ophthalmologic examination	X	Conducted by an ophthalmologist or optometrist (Section 11.5.5)
Complete 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 after subject has been at rest for at least 5 minutes (Section 11.5.4)
Multiple-breath washout	X	Performed pre- or post-bronchodilator, in multiple replicates, and before the spirometry assessment (Section 11.3.1)
Spirometry	X	Performed pre- or post-bronchodilator (Section 11.3.2)
Sweat chloride	X	Section 11.2
CF genotype (all subjects)	X	If the *CFTR* genotype result is not received before the first dose of study drug, a previous *CFTR* genotype laboratory report may be used to establish eligibility (Section 8.1). Subjects who have been enrolled and whose screening genotype does not confirm eligibility must be discontinued from the study (Section 9.9).
Serum pregnancy test (all female subjects)	X	Section 11.5.6
Serum chemistry	X	Section 11.5.2
Hematology	X	Section 11.5.2
Coagulation	X	Section 11.5.2
Urinalysis	X	Section 11.5.2
Medication review	X	Information regarding medications taken within 56 days before the Screening Visit will be collected (Section 9.5)
AEs and SAEs	Continuous from signing of ICF (and Assent Form) through Completion of Study Participation	Section 13.1; completion of study participation is defined in Section 9.1.6.

Table 3-1 Study VX19-445-116: Screening

Event/Assessment	Screening Visit Day -28 to Day -1	Comments

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

Table 3-2 Study VX19-445-116: Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1[b]	Day 3 ± 1 day	Day 15 ± 3 days	Week 4 ± 5 days	Week 8 ± 5 days	Week 12 ± 5 days	Week 16 ± 5 days	Week 20 ± 5 days	Week 24 ± 5 days	ETT Visit	Safety Follow-up[c] 28 (± 7) Days After Last Dose of Study Drug	Comments
Clinic Visit	X		X	X	X		X		X	X	X	
Telephone contact		X				X		X				Assess subject's status, any AEs, concomitant medications, treatments, and procedures.
Inclusion/ exclusion criteria review	X											Section 8
Randomization	X											Randomization may occur on either Day -1 or Day 1, after all eligibility criteria are confirmed.
Safety and Efficacy Assessments												
[redacted]												
Ophthalmologic examination									X at or up to 4 weeks before	X		Section 11.5.5
Height and weight	X		X	X	X		X		X	X	X	Measured before study drug dosing with shoes off

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

[b] To enter the Treatment Period, conditions for entry must be satisfied.

[c] 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 (Section 9.1.3).

Table 3-2 Study VX19-445-116: Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1[b]	Day 3 ± 1 day	Day 15 ± 3 days	Week 4 ± 5 days	Week 8 ± 5 days	Week 12 ± 5 days	Week 16 ± 5 days	Week 20 ± 5 days	Week 24 ± 5 days	ETT Visit	Safety Follow-up[c] 28 (± 7) Days After Last Dose of Study Drug	Comments
Vital signs and pulse oximetry	X		X	X	X		X		X	X	X	Performed after subject has been at rest for at least 5 minutes (Section 11.5.3)
Physical examination	X								X	X		Symptom directed physical examinations may be performed at any time if deemed necessary by the investigator (Section 11.5.3)
Standard 12-lead ECG	X				X		X		X	X	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)

Table 3-2 Study VX19-445-116: Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1[b]	Day 3 ± 1 day	Day 15 ± 3 days	Week 4 ± 5 days	Week 8 ± 5 days	Week 12 ± 5 days	Week 16 ± 5 days	Week 20 ± 5 days	Week 24 ± 5 days	ETT Visit	Safety Follow-up[c] 28 (± 7) Days After Last Dose of Study Drug	Comments
Sweat chloride	X		X	X	X		X		X	X		
Multiple-breath washout	X		X	X	X		X		X	X		Performed in multiple replicates, pre-bronchodilator, before the AM dose, and before spirometry assessment (Section 11.3.1).
[redacted]												
Observation 4 hours after the morning dose	X											Section 9.6.1
Pregnancy test (all female subjects)	urine		serum	serum	serum	urine	serum	urine	serum	serum	serum	At telephone contacts, a urine pregnancy test will be performed with a home kit provided by the study site. Results will be reported to the site by telephone (Section 11.5.6).
Serum chemistry	X		X	X	X		X		X	X	X	Section 11.5.2
Hematology	X		X	X	X		X		X	X	X	Section 11.5.2
Coagulation	X								X	X		Section 11.5.2

Table 3-2 Study VX19-445-116: Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1[b]	Day 3 ± 1 day	Day 15 ± 3 days	Week 4 ± 5 days	Week 8 ± 5 days	Week 12 ± 5 days	Week 16 ± 5 days	Week 20 ± 5 days	Week 24 ± 5 days	ETT Visit	Safety Follow-up[c] 28 (± 7) Days After Last Dose of Study Drug	Comments
Urinalysis	X								X	X		Section 11.5.2
AEs and SAEs	Continuous from signing of ICF (and Assent Form) through Completion of Study Participation											Section 13.1; completion of study participation is defined in Section 9.1.6.
Concomitant medications	Continuous from signing of ICF (and Assent Form) through Completion of Study Participation											Completion of study participation is defined in Section 9.1.6.
Concomitant treatment and procedures	Continuous from signing of ICF (and Assent Form) through Completion of Study Participation											Completion of study participation is defined in Section 9.1.6.
[redacted]												

Table 3-2 Study VX19-445-116: Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1[b]	Day 3 ± 1 day	Day 15 ± 3 days	Week 4 ± 5 days	Week 8 ± 5 days	Week 12 ± 5 days	Week 16 ± 5 days	Week 20 ± 5 days	Week 24 ± 5 days	ETT Visit	Safety Follow-up[c] 28 (± 7) Days After Last Dose of Study Drug	Comments
Study Drug Administration												
ELX/TEZ/IVA or placebo	Day 1 through evening before Week 24 Visit											Administered within approximately 30 minutes of consuming fat-containing food (e.g., standard "CF" meal or snack) (Section 9.6.1). On scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed (food to be provided by site on these days).

AE: adverse event; CF: cystic fibrosis; [redacted]; ECG: electrocardiogram; ELX: elexacaftor; ETT: early termination of treatment; ICF: informed consent form; IVA: ivacaftor; SAE: serious adverse event; TEZ: tezacaftor

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
β	beta, apparent elimination rate constant
BMI	body mass index
CF	cystic fibrosis
[redacted]	[redacted]
CFTR	CF transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
CI	confidence interval
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DMC	data monitoring committee
ECGs	electrocardiograms
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
ELX	elexacaftor
ETT	Early Termination of Treatment
EU	European Union
F/MF	*F508del* Mutation and a Minimal Function Mutation
F508del	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F/F	homozygous for *F508del*
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
$FEF_{25\%-75\%}$	forced expiratory flow, midexpiratory phase
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLI	Global Lung Function Initiative
GPP3	Good Publication Practices
GPS	Global Patient Safety
HBE	human bronchial epithelial
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
IA	interim analysis

Abbreviation	Definition
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IRB	institutional review board
IVA	ivacaftor
IWRS	interactive web response system
LCI	lung clearance index
$LCI_{2.5}$	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value
LS	least squares
LUM	lumacaftor
max	maximum value
MBW	multiple-breath washout
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function
min	minimum value
MMRM	mixed-effects model for repeated measures
N	size of subsample
N	total sample size
OATP1B1	organic anion transporting polypeptide 1B1
OATP1B3	organic anion transporting polypeptide 1B3
P	probability
PC	publication committee
PD	pharmacodynamics
PE	physical examination
PEx	pulmonary exacerbations
P-gp	P-glycoprotein
PIs	principal investigators
PK	pharmacokinetics
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PR	PR interval, segment
PT	preferred term
q12h	every 12 hours
qd	once daily
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTcF	QT corrected for HR
RD	respiratory domain
RNA	ribonucleic acid
RR	interval from the onset of 1 QRS complex to the next; use R-R if using with "intervals", i.e., "R-R interval"
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SC	steering committee
SD	standard deviation
SET	Study Execution Team
SI	SI units (International System of Units)
SOC	System Organ Class
SUSARs	suspected, unexpected, serious adverse reaction
SwCl	sweat chloride
TC	triple combination
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
ULN	upper limit of normal
US	United States

5 INTRODUCTION

5.1 Background

Cystic fibrosis (CF) is an autosomal recessive chronic disease with serious morbidities and frequent premature mortality. CF affects more than 70,000 individuals worldwide[1] (approximately 31,000 in the US[2] and 48,000 in the EU[3]). Based on its prevalence, CF qualifies as an orphan disease.[4, 5]

CF is caused by decreased quantity and/or function of the CFTR protein due to mutations in the *CFTR* gene.[6] CFTR is an ion channel that regulates the flow of chloride and other ions across epithelia in various tissues, including the lungs, pancreas and other gastrointestinal organs, and sweat glands.[7] Decreased CFTR quantity or function results in the failure to regulate chloride transport in these tissues leading to the multisystem pathology associated with CF.[8] In the lungs, obstruction of airways with thick mucus, establishment of a chronic bacterial infection in the airways, and damaging inflammatory responses are all thought to play a role in causing irreversible structural changes in the lungs, leading to respiratory failure. Progressive loss of lung function is the leading cause of mortality.[9]

The most common disease-causing *CFTR* mutation is *F508del.* Approximately 85% have at least 1 *F508del* allele.[10, 11]

Based on the understanding of the molecular defects caused by *CFTR* mutations, 2 complementary approaches have been developed to address the decreased quantity and/or function of CFTR in order to enhance chloride transport in patients with CF. Correctors facilitate the cellular processing and trafficking to increase the quantity of CFTR at the cell surface. Potentiators increase the channel open probability (channel gating activity) of the CFTR protein delivered to the cell surface to enhance ion transport. With differing mechanisms of action, a combination of correctors and potentiators increases F508del CFTR-mediated chloride transport more than either type of modulator alone.

The therapeutic activity of CFTR modulators has been established with products developed by Vertex Pharmaceuticals Incorporated and approved for the treatment of CF: ivacaftor (IVA) monotherapy (Kalydeco™), lumacaftor (LUM)/IVA (Orkambi®), and tezacaftor (TEZ)/IVA (Symdeko™/Symkevi®).

Elexacaftor (VX-445; ELX) is a next-generation CFTR corrector. In vitro, the triple combination (TC) of ELX, TEZ, and IVA (ELX/TEZ/IVA) increased CFTR chloride transport more than any of the dual combinations (ELX/TEZ, ELX/IVA, and TEZ/IVA) or individual components (ELX, TEZ, and IVA) when added to human bronchial epithelial (HBE) cells derived from 2 groups of CF patients: those heterozygous for *F508del* with a second *CFTR* allele carrying a minimal function (MF) mutation that is not responsive to IVA and TEZ/IVA (F/MF genotypes); and those homozygous for *F508del* (F/F genotypes). Pivotal Phase 3 studies in CF subjects aged 12 years and older with F/MF and F/F genotypes demonstrated that treatment with ELX/TEZ/IVA resulted in rapid, robust, clinically meaningful, and statistically significant improvements in all primary and key secondary efficacy and pharmacodynamic (PD) endpoints. ELX/TEZ/IVA was generally safe and well tolerated with a low rate of treatment discontinuation. Given the younger age group in this study, the effect of ELX/TEZ/IVA on endpoints [redacted] n this population may be different compared to older

populations. An open-label Phase 3 study is ongoing to evaluate the pharmacokinetics (PK), safety, and tolerability of ELX/TEZ/IVA in CF subjects aged 6 through 11 years of age.

Additional information about ELX/TEZ/IVA can be found in the Investigator's Brochure.

5.2 Study Rationale

Given the progressive nature of CF, there is a strong rationale for treating patients early in life. Vertex evaluated ELX/TEZ/IVA TC therapy in Phase 3 studies in adult and adolescent CF subjects with 1 or 2 copies of the *F508del* mutation, namely those with F/MF and F/F genotypes. In the 24-week placebo-controlled study in CF subjects with an F/MF genotype, there were clinically meaningful and statistically significant improvements in lung function ($ppFEV_1$), CFTR function (sweat chloride [SwCl]), respiratory symptoms (CFQ-R RD scores), and nutritional status (body mass index [BMI] and body weight), as well as a reduction in number of pulmonary exacerbations (PEx). The present study is designed to obtain placebo-controlled efficacy, safety, and PD information to expand the evaluation of ELX/TEZ/IVA in the pediatric population 6 through 11 years of age with F/MF genotypes.

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the efficacy of ELX/TEZ/IVA in subjects 6 through 11 years of age with CF, heterozygous for *F508del* and a MF mutation (F/MF)

6.2 Secondary Objectives

- To evaluate the PD of ELX/TEZ/IVA
- To evaluate the safety of ELX/TEZ/IVA

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Absolute change in lung clearance index$_{2.5}$ ($LCI_{2.5}$) from baseline through Week 24

7.2 Secondary Endpoints

- Absolute change in SwCl from baseline through Week 24
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, standard 12-lead electrocardiograms (ECGs), vital signs, pulse oximetry

[redacted]

8 STUDY POPULATION

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

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

8.1 Inclusion Criteria

1. Subject's legally appointed and authorized representative (e.g., parent or legal guardian) will sign and date informed consent form (ICF) and subject will sign an assent form (if applicable).
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Subjects (male and female) 6 through 11 years of age, inclusive, on the date of informed consent.
4. Subjects who weigh ≥15 kg without shoes at the Screening Visit.
5. Confirmed diagnosis of CF as determined by the investigator.
6. Subjects heterozygous for *F508del* and an MF mutation that is not responsive to IVA and TEZ/IVA (F/MF genotypes, Appendix A).
   - Genotype should be confirmed at the Screening Visit.
   - If the screening CFTR genotype result is not received before the first dose of study drug, a previous CFTR genotype laboratory report may be used to establish eligibility.
   - Subjects who have been enrolled and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).
7. Subjects with forced expiratory volume in 1 second (FEV_1) value ≥70% of predicted normal for age, sex, and height using equations of the Global Lung Function Initiative (GLI)[12] as determined by spirometry at screening (Section 11.3.2.
8. Subjects with a screening $LCI_{2.5}$ result ≥ 7.5 (Section 11.3.1).
9. Subjects with stable CF disease at the start of the Treatment Period as deemed by the investigator.
10. Subjects who are willing to remain on a stable CF medication regimen (other than *CFTR* modulators) through Week 24 or, if applicable, through the Safety Follow-up Visit
11. Subjects who are able to swallow tablets.
12. As judged by the investigator, the parent or legal guardian must be able to understand protocol requirements, restrictions, and instructions and the parent or legal guardian should be able to ensure that the subject will comply with and is likely to complete the study as planned.

8.2 Exclusion Criteria

1. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This includes, but is not limited to, the following:
   - Clinically significant 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)
   - Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN
   - Abnormal renal function defined as glomerular filtration rate ≤45◦mL/min/1.73◦m^2 (calculated by the Counahan-Barratt equation)[13]
4. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug).
5. Lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For subjects who have had a history of a positive culture, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
   - The subject has not had a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent.
   - The subject has had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent.
6. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug (Day 1).
7. Ongoing or prior participation in an investigational drug study (including studies investigating ELX with or without coadministration of other study drugs) within 28 days of the Screening Visit.
   - A washout period of 5 terminal half-lives of the previous investigational study drug, or 28 days, whichever is longer, must elapse before the Screening Visit.
   - The duration of the elapsed time may be longer if required by local regulations.
8. Use of restricted medication within specified duration before the first dose of study drug as defined in Table 9-2.

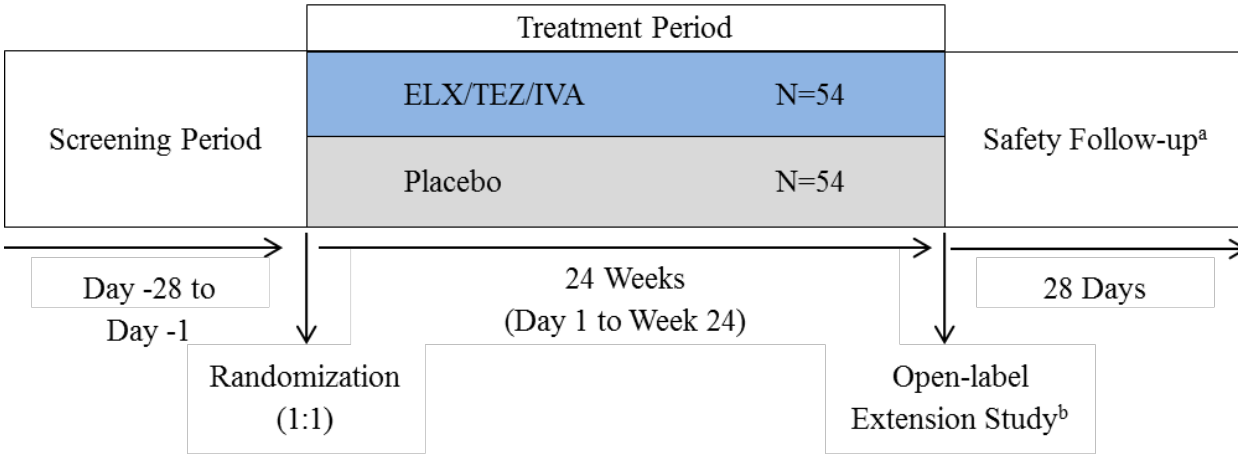
9. Pregnant and breast-feeding females. All female subjects regardless of childbearing potential status (Section 11.5.6) must have a negative pregnancy test at the Screening Visit and the Day 1 Visit.
10. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site.

9 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 3b, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in CF subjects aged 6 through 11 years who are heterozygous for the *F508del* mutation and a minimal function mutation (F/MF) (Figure 9-1).

Figure 9-1 VX19-445-116 Study Design



ELX: elexacaftor; IVA: ivacaftor; N: number of subjects; TEZ: tezacaftor

[a] The Safety Follow-up Visit is scheduled to occur 28 days (± 7 days) after the last dose.

[b] Subjects who complete the visits in the Treatment Period, regardless of whether they are on a treatment interruption, will be offered the opportunity to enroll in an optional open-label extension safety study evaluating ELX/TEZ/IVA. The Safety Follow-up Visit is not required for subjects who complete the Week 24 Visit and have enrolled in an open-label study within 28 days after the last dose of study drug.

Approximately 108 subjects will be randomized (1:1) to the ELX/TEZ/IVA group or the placebo group. The planned dosages to be evaluated are shown in Table 9-1.

Table 9-1 Treatment Period Groups and Dosages

Treatment Group Weight at Screening Visit	**ELX Dosage**	**TEZ Dosage**	**IVA Dosage**
ELX/TEZ/IVA			
<30 kg	100 mg qd	50 mg qd	75 mg q12h
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
Placebo	0 mg	0 mg	0 mg

ELX: elexacaftor; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor
Note: Study drug administration is described in Section 9.6.

Randomization will be stratified by $LCI_{2.5}$ determined at the Screening Visit (<10 versus ≥10) and weight at the Screening Visit (<30 kg versus ≥30 kg).

9.1.1 Screening

Screening Visit assessments are listed in Table 3-1.

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

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

9.1.1.1 Repetition of Screening 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 re-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)

9.1.2 Treatment Period

The Treatment Period will last approximately 24 weeks. Study drug administration details are provided in Section 9.6.

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

9.1.3 Follow-up

The Safety Follow-up Visit is scheduled to 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 open-label extension safety study will be available for subjects who complete the last treatment period visit and are eligible. 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 drug treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the decision to discontinue treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit (Table 3-2) if applicable (Section 9.1.3).

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

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 3-2.

Subjects who prematurely discontinue treatment are not eligible to enroll in the optional open-label extension safety study.

9.1.5 Lost to Follow-up

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

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

9.1.6 Completion of Study Participation

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

- 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 9.9)

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

The end of study is defined in Section 13.2.8.

9.1.7 Data Monitoring Committee

A data monitoring committee (DMC) will be formed. The DMC objectives and operational details will be defined in a separate document (DMC Charter), which will be finalized before the first subject is screened. The DMC will conduct regular planned reviews of study data as outlined in the DMC Charter.

9.2 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized (1:1) to the ELX/TEZ/IVA or placebo group. Randomization will be stratified by $LCI_{2.5}$ determined at the Screening Visit (<10 versus ≥10) and weight at the Screening Visit (<30 kg versus ≥30 kg).

An interactive web response system (IWRS) will be used to assign subjects to treatment. 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 (SET).

9.3 Rationale for Study Elements

9.3.1 Study Design

A randomized, double-blind, placebo-controlled study design was selected to ascertain the effects of ELX/TEZ/IVA through between-group comparisons while avoiding observer bias. Placebo is considered the appropriate comparator because no CFTR modulator regimen has been approved for use in subjects 6 through 11 years of age who have F/MF genotypes.

The rationale for including absolute change in $LCI_{2.5}$ from baseline through Week 24 as the primary endpoint is discussed in Section 9.3.4.

9.3.2 Study Population

This study will enroll CF subjects with F/MF genotypes, 6 through 11 years of age. ELX/TEZ/IVA is expected to provide clinical benefit to these patients based on the results of a Phase 3 study (Study VX17-445-102), which demonstrated the efficacy and safety of ELX/TEZ/IVA in CF subjects ≥12 years of age who have F/MF genotypes.

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

9.3.3 Study Drug Dose and Duration

Study Drug Dose

The dose of ELX/TEZ/IVA evaluated in the pivotal Phase 3 study in subjects with F/MF genotypes ≥12 years of age (200 mg qd/100 mg qd/150 mg q12h) was generally safe and well tolerated and resulted in clinically meaningful improvements compared to placebo in endpoints including $ppFEV_1$ (LS mean treatment difference of 14.3 percentage points [p<0.0001] for

absolute change from baseline) and SwCl (LS mean treatment difference of -41.8 mmol/L [p<0.0001] for absolute change from baseline) through 24 weeks.

The doses of ELX/TEZ/IVA administered in this study (200 mg qd/100 mg qd/150 mg q12h for subjects ≥30 kg, 100 mg qd/50 mg qd/75 mg q12h for subjects <30 kg) have been selected through assessment of PK over approximately 2 weeks in Part A of a registrational Phase 3 study in 6 to 11 year of age CF subjects, and are the same doses being administered over 24 weeks in Part B of that registrational study.

Treatment Duration

This study will have a 24-week treatment duration to allow for placebo-controlled assessment of safety and efficacy over 24 weeks of treatment.

9.3.4 Rationale for Study Assessments

Most of the safety, efficacy, and PD assessments are standard parameters for clinical studies in drug development and are generally recognized as reliable, accurate, and relevant to the study of subjects with CF. Baseline and follow-up ophthalmologic examinations are recommended for monitoring of pediatric patients treated with IVA-containing drug regimens, and have been added to the standard safety assessments.

LCI is a measure of ventilation inhomogeneity assessed by multiple-breath washout (MBW) that is based on tidal breathing techniques that have been evaluated in patients as young as infants.[14, 15] Studies have shown that LCI correlates with FEV_1 in its ability to measure airway disease and can detect lung disease at an earlier stage than spirometry.[16, 17]

9.4 Study Restrictions

9.4.1 Prohibited Medications

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

Table 9-2 Prohibited Medications

	Timing of Restriction		
Medication	**Start of Restriction**	**End of Restriction**	**Rationale**
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through completion of study participation	ELX, TEZ, and IVA are metabolized extensively via CYP3A4. Therefore, use of moderate and strong inducers and inhibitors of CYP3A, which have the potential to alter the exposure of ELX, TEZ, or IVA, will be prohibited.
Moderate and strong CYP3A inhibitors (except ciprofloxacin)[a]	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through completion of study participation	
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.

Table 9-2 Prohibited Medications

Medication	Timing of Restriction: Start of Restriction	Timing of Restriction: End of Restriction	Rationale

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

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

9.5 Prior and Concomitant Medications

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

For subjects who are screened but are not subsequently enrolled, details of prior medication will be documented only in the 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 11.3.2.

9.6 Administration

9.6.1 Dosing

Study drug tablets will be administered orally as shown in Table 9-3. Subjects in both treatment groups (ELX/TEZ/IVA and placebo) will receive the same number of tablets each day to maintain the blind. Additional information is provided in the Pharmacy Manual.

Table 9-3 Study Drug Administration

Subject Weight at Screening	Tablet Strength	Time	Number of Tablets Taken
<30 kg	50-mg ELX/25-mg TEZ/37.5-mg IVA	AM	2 tablets
	75-mg IVA	PM	1 tablet
≥30 kg	100-mg ELX/50-mg TEZ/75-mg IVA	AM	2 tablets
	150-mg IVA	PM	1 tablet

ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

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. At the Day 1 Visit, all subjects will be observed for 4 hours after the morning dose of the study drug.
4. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. The meal or snack will be provided by the site for the morning dose of study drug.
5. For visits after the Day 1 Visit, subjects will be instructed to bring all used and unused study drug to the site; study drug will be dispensed at each visit, as appropriate.
6. At the Week 24 Visit, the morning dose of study drug will NOT be administered. The last dose of study drug will be the evening dose administered the day before the Week 24 Visit.

9.6.2 Missed Doses

If 6 hours or less have passed since the missed morning or evening dose, the patient 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 patient 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 patient should not take the missed dose. The next scheduled morning dose should be taken at the usual time.

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

9.7 Dose Modification for Toxicity

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

9.8 Study Drug Interruption and Stopping Rules

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

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

9.8.1 Liver Function Tests

The central laboratory will notify the medical monitor of 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.

9.8.2 Rash

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

9.9 Removal of Subjects

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

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

- Has a screening CFTR genotype that does not confirm study eligibility if a previous CFTR genotype laboratory report was used to establish eligibility. These subjects must be discontinued from the study (Section 8.1)
- Meets any of the stopping (discontinuation) criteria (Section 9.8)

- Becomes pregnant (Section 11.5.6.2)

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

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for an ETT Visit and Safety Follow-up Visit, if applicable (see Section 9.1.4), and follow up with the subject regarding any unresolved AEs.

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

9.10 Replacement of Subjects

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

10 STUDY DRUG INFORMATION AND MANAGEMENT

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

10.1 Preparation and Dispensing

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

10.2 Packaging and Labeling

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

10.3 Study Drug Supply, Storage, and Handling

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

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

Drug Name, Dosing Form, Route	Tablet Strength	
	Subjects <30 kg at Screening	Subjects ≥30 kg at Screening
ELX/TEZ/IVA, FDC tablet, oral		
ELX	50 mg	100 mg
TEZ	25 mg	50 mg
IVA	37.5 mg	75 mg
ELX/TEZ/IVA-matching placebo, tablet, oral	0 mg	0 mg
IVA, tablet, oral	75 mg	150 mg
IVA-matching placebo, tablet, oral	0 mg	0 mg

ELX: elexacaftor; FDC: fixed-dose combination; IVA: ivacaftor; TEZ: tezacaftor
Note: See Table 9-3 for details on study drug administration.

10.4 Drug Accountability

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

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

10.5 Disposal, Return, or Retention of Unused Drug

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

10.6 Compliance

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

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

10.7 Blinding and Unblinding

This will be a double-blind study.

10.7.1 Blinding

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

Individuals who may be unblinded include only the following:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the subject and her fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations
- Vendor preparing the final (production) randomization list
- Vertex IWRS Manager
- Vertex Clinical Supply Chain
- DMC
- Vendor preparing the unblinded analysis for safety review by the DMC

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

Shortly before any planned efficacy analysis is conducted, the MBW, 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 MBW results until Vertex has determined that the study has completed (i.e., clinical study report [CSR] finalization), regardless of whether the subject has prematurely discontinued treatment.

10.7.2 Unblinding

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

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

Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators will use their best judgment as to whether to unblind without first attempting to contact the medical monitor to discuss unblinding.

If investigators deem it unnecessary to unblind immediately, they will first attempt to contact the medical monitor to discuss unblinding. If investigators have tried but are unable to reach the medical monitor, they will use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding.

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

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

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

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

Unblinding: Interim Analysis

A limited Vertex team may be unblinded if an IA is performed. Members of the limited Vertex unblinded team will not be involved in or influence the conduct of the remaining part of the study to protect the integrity of the study (Section 12.3.5.1) Subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team will remain blinded to subject-level data until the final database lock.

11 ASSESSMENTS

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

[redacted]

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 Pharmacodynamics: Sweat Chloride

The sweat chloride 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 sweat chloride test results will not be disclosed to the study sites. Specific instructions for collection, handling, processing, and shipping of sweat chloride samples to the central laboratory will be provided separately. The sweat chloride 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 for information about access to SwCl results.

11.3 Efficacy

11.3.1 Multiple-breath Washout

The N_2-MBW testing will be performed in multiple replicates for each visit and the final LCI value will be calculated from the technically acceptable washout replicates by a central reader. The final LCI value at each visit will be the value provided by the LCI vendor based on the replicates.

During the Screening Period, the MBW test may be performed pre- or post-bronchodilator. At all other visits, all MBW tests should be performed pre-bronchodilator as described in Section 11.3.2. The MBW test should be performed before the spirometry assessment (Section 11).

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

11.3.2 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines/European Respiratory Society Guidelines[18] and according to the additional guidelines that follow.

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

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

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

[redacted]

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

[redacted]

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

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

[redacted]

[redacted]

11.5 Safety

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

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

11.5.1 Adverse Events

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

11.5.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory 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 kit. All blood samples will be collected while subjects are in a seated or supine position. Specific instructions for the collection, processing, and shipment of samples will be provided in a separate Laboratory Manual.

Laboratory test results that are abnormal and considered clinically significant must be reported as AEs (see Section 13.1.1.2).

Blood and urine samples for clinical laboratory assessments will be collected according to the schedule of assessments (Table 3-1 and Table 3-2).

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		
Triglycerides		
Low-density lipoprotein-direct		
High-density lipoprotein		

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

[a] If urinalysis results are positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be done, and results will be provided for leukocytes, erythrocytes, crystals, bacteria, and casts.

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

Pregnancy (β-human chorionic gonadotropin) Tests for all Female Subjects: All female subjects must have a serum pregnancy test at screening. Serum pregnancy tests will be performed at the study site and analyzed at the central laboratory. Urine pregnancy tests will either be performed and analyzed at the site or, when there is no clinic visit scheduled, at home by using a home kit provided by the site. Results will be reported to the site by telephone. The urine pregnancy test on Day 1 must be negative before the first dose of study drug is administered to the subject. Additional pregnancy tests may be required according to local regulations and/or requirements.

CF genotype (Screening Period only): CF genotyping will be performed on all subjects to confirm the genotype documented in the subject's medical record.

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 and Vital Signs

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

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

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

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

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

11.5.4 Electrocardiograms

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

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

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 QTcF is increased by >60 msec from the baseline or an absolute QTcF value is ≥500 msec for any scheduled ECG, 2 additional ECGs will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>60 msec from baseline or ≥500 msec), a single ECG will be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

11.5.5 Ophthalmologic Examination

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

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

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

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

In addition to the screening ophthalmologic examination, all subjects who have completed at least 12 weeks of study drug treatment will have a single follow-up ophthalmologic examination. This examination should be completed at or up to 4 weeks before the Week 24 Visit, unless the subject prematurely discontinues study drug, in which case this examination should occur by the Safety Follow-up Visit (or ETT Visit for subjects who do not complete a Safety Follow-up Visit), as described in Table 3-2.

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 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 subject is male and is infertile (e.g., bilateral orchiectomy). If a male subject is assumed to have complete bilateral absence of the vas deferens, infertility must be documented before the first dose of study drug (e.g., examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound).
- If the subject is female and is of non-childbearing potential. To be considered of non-childbearing potential, the female must meet at least 1 of the following criteria:
    - Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females
    - Documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy

Note: All other females (including females with tubal ligations and pre-menarchal females) will be considered to be of childbearing potential.

- Same-sex relationships

For subjects for whom the contraception requirement is not waived, study participation requires a commitment from the subject that at least 1 acceptable method of contraception is used. 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

	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
Hormone-releasing	Yes	Yes
Non-hormone releasing	Yes	Yes
Oral, implanted, injected, or vaginal hormonal contraceptives, if successfully used for at least 60 days before the first dose of study drug.	Yes	Yes

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

Additional notes:

- If over the course of the study the subject meets the criteria for waiving the contraception requirements, the subject does not need to follow the contraceptive methods listed in Table 11-2.
- If over the course of the study the subject's status changes and the subject does not meet the criteria for waiving the contraception requirements, the subject must begin following the contraceptive methods listed in Table 11-2.
- Male subjects must not donate sperm during the period starting from the first dose of study drug until 90 days after the last dose of study drug.
- Female subjects should not nurse a child during the period starting from the first dose of study drug until 90 days after the last dose of study drug.
- Female partners of male subjects should not plan to become pregnant during the study or within 90 days after the last dose of study drug, with the exception of those 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 subject, or the female partner of a male 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.

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

12 STATISTICAL AND ANALYTICAL PLANS

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

12.1 Sample Size and Power

Approximately 108 subjects will be enrolled and randomized (1:1) to the ELX/TEZ/IVA group or the placebo group.

Power for Primary Efficacy Endpoint

The primary efficacy endpoint is the absolute change in $LCI_{2.5}$ from baseline through Week 24. The primary null hypothesis to be tested is that the mean absolute change in $LCI_{2.5}$ from baseline through Week 24 is the same for the 2 treatment groups, ELX/TEZ/IVA and placebo. The null hypothesis will be tested at a 2-sided significance level of 0.05.

Assuming a within-group SD of 1.5 and a treatment difference of -1.0 between ELX/TEZ/IVA and placebo, a sample size of 49 subjects completing the Treatment Period in each group for a total of 98 subjects will have approximately 90% power for the $LCI_{2.5}$ hypothesis testing, based on a 2-sided 2-sample t-test at a significance level of 0.05. Assuming a 10% dropout rate, approximately 108 subjects will be enrolled.

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 CFTR allele mutation and received at least 1 dose of study drug. The FAS will be used to summarize subject demographics

and baseline characteristics, and for analyses of all efficacy and PD endpoints 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 actually received, unless otherwise specified.

12.3 Statistical Analysis

12.3.1 General Considerations

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

Categorical variables will be summarized using counts and percentages.

Treatment-emergent (TE) period will include the time from the first dose of study drug in the Treatment Period (ELX/TEZ/IVA or placebo) through 28 days after the last dose or the completion of study participation date (as defined in Section 9.1.6), whichever occurs first.

Baseline unless otherwise specified, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug. For ECG, baseline will be defined as the most recent pretreatment measurement, or the average of triplicate measurements if the most recent pretreatment measurement is obtained in triplicate, before the first dose of study drug.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

The number and percentage of subjects in each disposition category (e.g., randomized, included in the FAS, included in the Safety Set, completed Treatment Period, completed study, prematurely discontinued treatment or study with a breakdown of the reasons for discontinuation, and entered an open-label study) will be summarized by treatment group.

12.3.2.2 Demographics and Baseline Characteristics

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

The following demographics and baseline characteristics will be summarized by treatment group for the FAS, and will include (but are not limited to): sex, race, age, weight, height, BMI, $LCI_{2.5}$, $ppFEV_1$, and SwCl.

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

12.3.2.3 Prior and Concomitant Medications

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

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

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

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

12.3.2.4 Study Drug Exposure and Compliance

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

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

12.3.3 Efficacy and Pharmacodynamic Analysis

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

12.3.3.1 Analysis of Primary Endpoint

The primary efficacy endpoint is the **absolute change in $LCI_{2.5}$ from baseline through Week 24**. The analysis of this endpoint will be performed using a mixed-effects model for repeated measures (MMRM) with absolute change from baseline in $LCI_{2.5}$ at each post-baseline visit as the dependent variable. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects, and will be adjusted for main covariates as appropriate. Details will be described in the SAP. The primary result obtained from the model will be the estimated treatment difference through Week 24 (defined as the average of Weeks 4, 8, 16, 24), with a 2-sided 95% CI and a 2-sided *P* value provided. The treatment difference at each post-baseline visit, obtained from the mode, will also be provided.

[redacted]

12.3.3.2 Analysis of Secondary Endpoints

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

The analysis of this pharmacodynamic endpoint will be based on an MMRM model similar to the analysis of the primary endpoint above, with absolute change from baseline in SwCl at each post-baseline visit as the dependent variable.

The primary result obtained from the model will be the estimated treatment difference through Week 24. The LS mean estimate with a 2-sided 95% CI and a 2-sided *P* value will be provided. The treatment difference at each post-baseline visit, obtained from the model, will also be provided.

[redacted]

12.3.4 Safety Analysis

All safety analyses will be based on the data from the TE period for all subjects in the Safety Set. The overall safety profile of study drug will be assessed in terms of the following safety and tolerability assessments:

- 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

Safety assessments will be analyzed based on the Safety Set. Only a descriptive analysis of safety will be performed.

12.3.4.1 Adverse Events

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

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

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

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

- Overview of TEAEs
- TEAEs and related TEAEs
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Serious TEAEs and related serious TEAEs
- Grade 3 and Grade 4 TEAEs

Summaries will be presented by MedDRA System Organ Class and Preferred Term using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once, only the maximum severity level will be presented in the severity summaries, and the strongest relationship level in the relationship summaries.

Listings containing individual subject level AE data will be provided separately for:

- Serious TEAEs
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- TEAEs leading to death

In addition, all AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

12.3.4.2 Clinical Laboratory Assessments

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

For threshold analysis, the number and percentage of subjects meeting threshold criteria during the TE Period will be summarized by treatment group. Shift analysis from baseline to post-baseline will also be conducted by treatment group for selected laboratory parameters. The threshold criteria and selected parameters will be provided in the SAP.

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

12.3.4.3 Electrocardiogram

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

For threshold analysis, the number and percentage of subjects meeting threshold criteria during the TE Period will be summarized by treatment group. The threshold criteria will be provided in the SAP.

12.3.4.4 Vital Signs

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

For threshold analysis, the number and percentage of subjects meeting threshold criteria during the TE Period will be summarized by treatment group. The threshold criteria will be provided in the SAP.

12.3.4.5 Pulse Oximetry

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

Shift analysis from baseline to the lowest value of the percent of oxygen saturation during the TE Period will be performed by treatment group.

12.3.4.6 Ophthalmologic Examinations

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

12.3.4.7 Physical Examination

PE findings will be presented in individual subject data listings only.

12.3.5 Interim and Data Monitoring Committee Analyses

12.3.5.1 Interim Analysis

An optional interim analysis (IA) may be conducted during the study at the discretion of the sponsor. In the event that an IA is performed, multiplicity adjustment will be applied to control for family-wise type I error rate, and the details will be provided in the SAP.

12.3.5.2 Data Monitoring Committee Analysis

The DMC will conduct regularly planned safety reviews of study data. Details of the safety reviews will be described in the DMC charter.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

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

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

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

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

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

13.1.1.3 Documentation of Adverse Events

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

All subjects will be queried, using nonleading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms will be identified as 1 overall event or diagnosis. All AEs for enrolled subjects will be recorded in the CRF and source document. AEs for subjects who are screened but not subsequently enrolled 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: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials, September 2007, Center for Biologics Evaluation and Research, https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM091977.pdf (Accessed September 2019). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." When considering the severity of an AE in a pediatric subject, the investigator will consider that reference ranges for pediatric clinical laboratory parameters may differ from those in the CTCAE. The severity of an AE described by a term that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

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

Source: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed September 2019)
ADL: activities of daily living; AE: adverse event

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

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

AE: adverse event

13.1.1.7 Adverse Event Outcome

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

Table 13-4 Classifications for Outcome of an AE

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

Table 13-4 Classifications for Outcome of an AE

Classification	Definition

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: [redacted] (preferred choice)

Fax: [redacted]

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

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

13.1.2.3 Expedited Reporting and Investigator Safety Letters

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

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

13.2 Administrative Requirements

13.2.1 Ethical Considerations

The study will be conducted in accordance with the current ICH 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.

13.2.2 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject or legal representative or guardian (if applicable), and assent will be obtained from the subject (if applicable), before study participation. The method of obtaining and documenting the informed consent and assent (if applicable) and the contents of the consent will comply with current ICH E6 GCP Guidelines and all applicable laws and regulations and will be subject to approval by Vertex or its designee. When determining the age of the subject, other study eligibility criteria, and timing of collection applicable assessments, the informed consent will be used as the reference (e.g., age at time of informed consent, date of informed consent, timing of AE collection).

13.2.3 Investigator Compliance

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

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

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

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

13.2.6 Record Retention

The investigator will maintain all study records according to 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.

13.2.7 Study Termination

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

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

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

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

13.2.8 End of Study

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

13.3 Data Quality Assurance

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

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each subject. Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure,

validated, web-based electronic data capture (EDC) application. Vertex will have read-only access to site-entered clinical data in the EDC application.

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

13.4 Monitoring

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

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

13.5 Electronic Data Capture

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

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

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

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

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

13.6 Confidentiality and Disclosure

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

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

13.7 Publications and Clinical Study Report

[redacted]

13.7.2 Clinical Study Report

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

14 REFERENCES

1 Cystic Fibrosis Foundation. What is cystic fibrosis? Available at: https://www.cff.org/What-is-CF/About-Cystic-Fibrosis/. Accessed 22 March 2018.

2 Cystic Fibrosis Foundation. 2018 Patient Registry Annual Data Report. Bethesda, MD: 2019.

3 European Cystic Fibrosis Society. 2017 ECFS Patient Registry Annual Data Report. Karup, Denmark: 2019.

4 United States Department of Health and Human Services. Food and Drug Administration. Office of Orphan Products Development. Developing Products for Rare Diseases & Conditions. Available at: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm. Accessed 19 September 2016.

5 European Medicines Agency [Internet]. Committee for Orphan Medicinal Products (COMP). Available at: https://www.ema.europa.eu/en/committees/committee-orphan-medicinal-products-comp. Accessed 07 December 2018.

6 Rommens JM, Iannuzzi MC, Kerem B, Drumm ML, Melmer G, Dean M, et al. Identification of the cystic fibrosis gene: chromosome walking and jumping. Science. 1989;245(4922):1059-65.

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

8 Sheppard MN, Nicholson AG. The pathology of cystic fibrosis. Curr Diagn Pathol. 2002;8(1):50-59.

9 Flume PA, VanDevanter DR. State of progress in treating cystic fibrosis respiratory disease. BMC Med. 2012;10:88.

10 Cystic Fibrosis Foundation. 2017 Patient Registry Annual Data Report. Bethesda, MD: 2018.

11 European Cystic Fibrosis Society. 2016 ECFS Patient Registry Annual Data Report. Karup, Denmark: European Cystic Fibrosis Society; 2018.

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

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

14 Horsley A. Lung clearance index in the assessment of airways disease. Respir Med. 2009;103(6):793-99.

15 Sinhal S, Galati J, Baldwin DN, Stocks J, Pillow JJ. Reproducibility of multiple breath washout indices in the unsedated preterm neonate. Pediatr Pulmonol. 2010;45(1):62-70.

16 Lum S, Gustafsson P, Ljungberg H, Hulskamp G, Bush A, Carr SB, et al. Early detection of cystic fibrosis lung disease: multiple-breath washout versus raised volume tests. Thorax. 2007;62(4):341-47.

17 Gustafsson PM, De Jong PA, Tiddens HA, Lindblad A. Multiple-breath inert gas washout and spirometry versus structural lung disease in cystic fibrosis. Thorax. 2008;63(2):129-34.

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

[redacted]

22 Wenninger K, Aussage P, Wahn U, Staab D, German Cystic Fibrosis Questionnaire study group. The revised German Cystic Fibrosis Questionnaire: validation of a disease-specific health-related quality of life instrument. Qual Life Res. 2003;12(1):77-85.

23 Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. Ann Intern Med. 2015;163(6):461-4.

24 International Committee of Medical Journal Editors (ICMJE). December 2017. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Available at: http://www.icmje.org/recommendations/. Accessed 03 August 2018.

APPENDIX A Eligible MF *CFTR* Mutations

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

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

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

Inclusion of MF Mutations Based on In Vitro Testing

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

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

Eligible MF Mutations

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

Non-exhaustive List of Minimal Function *CFTR* Mutations Eligible for VX19-445-116

Q2X	L218X	Q525X	R792X	E1104X
S4X	Q220X	G542X	E822X	W1145X
W19X	Y275X	G550X	W882X	R1158X
G27X	C276X	Q552X	W846X	R1162X
Q39X	Q290X	R553X	Y849X	S1196X
W57X	G330X	E585X	R851X	W1204X
E60X	W401X	G673X	Q890X	L1254X
R75X	Q414X	Q685X	S912X	S1255X
L88X	S434X	R709X	Y913X	W1282X
E92X	S466X	K710X	Q1042X	Q1313X
Q98X	S489X	Q715X	W1089X	Q1330X
Y122X	Q493X	L732X	Y1092X	E1371X
E193X	W496X	R764X	W1098X	Q1382X
W216X	C524X	R785X	R1102X	Q1411X

185+1G>T	711+5G>A	1717-8G>A	2622+1G>A	3121-1G>A
296+1G>A	712-1G>T	1717-1G>A	2790-1G>C	3500-2A>G
296+1G>T	1248+1G>A	1811+1G>C	3040G>C (G970R)	3600+2insT
405+1G>A	1249-1G>A	1811+1.6kbA>G		3850-1G>A
405+3A>C	1341+1G>A	1811+1643G>T	3120G>A	4005+1G>A
406-1G>A	1525-2A>G	1812-1G>A	3120+1G>A	4374+1G>T
621+1G>T	1525-1G>A	1898+1G>A	3121-2A>G	
711+1G>T		1898+1G>C		

182delT	1119delA	1782delA	2732insA	3791delC
306insA	1138insG	1824delA	2869insG	3821delT
365-366insT	1154insTC	1833delT	2896insAG	3876delA
394delTT	1161delC	2043delG	2942insT	3878delG
442delA	1213delT	2143delT	2957delT	3905insT
444delA	1259insA	2183AA>G [a]	3007delG	4016insT
457TAT>G	1288insTA	2184delA	3028delA	4021dupT
541delC	1343delG	2184insA	3171delC	4022insT
574delA	1471delA	2307insA	3171insC	4040delA
663delT	1497delGG	2347delG	3271delGG	4279insA
849delG	1548delG	2585delT	3349insT	4326delTC
935delA	1609del CA	2594delGT	3659delC	
1078delT	1677delTA	2711delT	3737delA	

Non-exhaustive List of Minimal Function *CFTR* Mutations Eligible for VX19-445-116

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

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

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

[a] Also known as 2183delAA>G.

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #:	VX19-445-116	Version #:	1.0	Version Date:	18 December 2019
Study Title: A Phase 3b, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 6 Through 11 Years of Age Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)					

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

Printed Name	Title
Signature	Date

15.2 Investigator Signature Page

Protocol #:	VX19-445-116	Version #:	1.0	Version Date:	18 December 2019
Study Title: A Phase 3b, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 6 Through 11 Years of Age Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)					

I have read Protocol VX19-445-116, Version 1.0, and agree to conduct the study according to its terms. I understand that all information concerning elexacaftor (ELX), tezacaftor (TEZ), and ivacaftor (IVA) and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date

1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol Addendum for Cystic Fibrosis

Cystic Fibrosis Studies for the Following Programs

Ivacaftor (VX-770)

[redacted]

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

[redacted]

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

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

Summary of Changes to Cystic Fibrosis Clinical Study Protocols

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

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

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

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

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

Protocol Change	Rationale for Change	Study Number
Addendum Version 3.0, dated 29 July 2020		
Assessments Unscheduled visit(s) will be permissible at the discretion of the investigator(s) or Vertex. The unscheduled visit(s) may be conducted at any time during the study (including after the protocol defined last study visit) in the event assessments specified to be collected at a scheduled visit were not collected due to COVID-19.	To ensure subject safety and/or to facilitate evaluation of safety and/or efficacy if assessments are not performed per the schedule in the protocol due to COVID-19.	[redacted] [redacted] [redacted] [redacted] VX19-445-116 [redacted] [redacted]
Implementaion of measures described in addenda versions 1.0 and 2.0, as applicable.	To ensure subject safety and/or to facilitate evaluation of safety and/or efficacy while maintaining study integrity and the safety of subjects and site personnel.	

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

Protocol Change	Rationale for Change	Study Number
Addendum Version 2.0, dated 15 May 2020		
Assessments Weight and height/length/stature may be assessed by subjects or their caregivers using medical grade scales and stadiometers, as indicated per protocol and per local regulation. Sites and subjects will receive training and guidance as needed on these devices. Subjects or caregivers will provide these measurements to site personnel by telephone or video call. Investigators will review results and contact subjects for follow-up as needed. All data will continue to be retained in the subject's source files.	To allow for collection of key data to assess safety and/or efficacy while maintaining study integrity and the safety of subjects and site personnel. *Addendum 1 allowed for these assessments to be performed by qualified personnel conducting the in-home visits. Addendum 2 allows for these assessments to be performed by subjects or caregivers.*	[redacted] [redacted] [redacted] [redacted] VX19-445-116 [redacted] [redacted]

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

Protocol Change	Protocol Change	Protocol Change
Addendum Version 1.0, dated 24 April 2020		
Consenting of Subjects ICFs may be provided electronically or by post mail to subjects (and/or caregivers, as indicated per protocol). The subjects and/or caregivers will review the ICF with an appropriately qualified member of the investigator's team via telephone contact or video call. After this review, subjects and/or caregivers will consent (or assent, if applicable), and/or reconsent verbally and by signing and dating the ICF and returning it to the site via post mail. The signed and dated ICF will then be signed and dated by the investigator. Subjects participating in select studies may have the opportunity to enroll in longterm extension studies. Informed consent (or assent, if applicable), and/or reconsent for subjects (and/or caregivers, as indicated per protocol) may be obtained per the same process described above, as applicable.	To provide alternative methods of obtaining reconsent or consent, as applicable, while ensuring subject safety.	[redacted]
Study Drug Shipping Study drug may be shipped directly from the site to the subject, as applicable, and if permitted by local regulations; subject protected health information will not be released to Vertex. Reconciliation, return, and destruction of study drug will continue to occur at the clinical site as indicated per protocol and in adherence to local regulations.	To ensure subjects can continue treatment with study drug without interruption while ensuring their safety. To clarify that despite these alternative measures, reconciliation, return, and destruction of study drug will remain as indicated per protocol.	[redacted] VX19-445-116
In-home Visits and/or Telephone Contact Study visits may be conducted as in-home visits by qualified personnel as requested by participating sites on a per-subject basis. In addition, all subjects may be contacted by site personnel by telephone or video call, irrespective of in-home visits.	To provide subjects the opportunity to continue participation in the clinical studies while ensuring their safety by minimizing the risk to COVID-19 exposure through travel.	[redacted] for telephone contact only

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

Protocol Change	Protocol Change	Protocol Change
Addendum Version 1.0, dated 24 April 2020		
Safety Assessments and Reporting Safety assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits (e.g., personnel from site or qualified health care agency). These assessments may include the following, as indicated per protocol, and per local regulation: • vital signs • pulse oximetry • height/length/stature • weight • physical examination (complete or abbreviated) • pregnancy test (serum or urine) • urinalysis • blood draws for safety test panels (chemistry, LFT panel, lipid panel, hematology, coagulation). Blood and/or urine samples for safety assessments are analyzed as indicated per protocol for subjects who have in-home visits. Blood and/or urine samples for safety assessments may be collected and analyzed at local laboratories for subjects who do not have in-home visits, but do not complete the assessment at the site. In addition, safety assessents will be evaluated by telephone. These assessments may include the review of the following: • AEs • signs and symptoms/systems for CF • medications • planned or unplanned hospitalizations for CF • study drug administration • outcomes related to PEx • outcomes related to antibiotic treatment Investigators will review results (in-home and telephone) and contact subjects for follow-up as needed. All data will continue to be retained in the subject's source files. Any clinically significant finding (e.g., AE, SAE, laboratory abnormalities) will continue to be reported as indicated per protocol.	To assess the safety and tolerability of the CFTR modulator evaluated in the specific clinical study while ensuring subject safety. These safety assessments will continue to provide safety data while minimizing burden to subjects and site personnel. To clarify that despite these alternative measures, all adverse events and serious adverse events should be reported as indicated per protocol.	[redacted] [redacted] [redacted] [redacted] VX19-445-116 [redacted] [redacted] [redacted] for telephone contact and blood samples collected and analyzed at local laboratories

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

Protocol Change	Protocol Change	Protocol Change
Addendum Version 1.0, dated 24 April 2020		
Efficacy and Other Assessments Efficacy and other assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits. These assessments may include the following, as indicated per protocol, and per local regulation. In-home Spirometry Assessment A spirometry device may be provided to subjects for in-home assessments of lung function as indicated per protocol. Sites and subjects will receive training and guidance as needed. [redacted] Other Assessments • ECGs • sweat chloride • blood samples for *CFTR* genotype testing, [redacted] PK, FSH, [redacted]	To be able to assess safety, treatment effectiveness, and quality of life measures of the CFTR modulator evaluated in the specific clinical study while ensuring subject safety.	All Efficacy and Other Assessments [redacted] VX19-445-116 [redacted]

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

Protocol Change	Protocol Change	Protocol Change
Addendum Version 1.0, dated 24 April 2020		
Remote Monitoring Vertex has implemented remote monitoring visits where applicable, including remote source data verification, as allowed per local regulations. Remote monitoring will focus on collection of safety data, and data supporting primary and key secondary endpoints.	To allow for review of key data to inform on the safety of subjects receiving treatment. To allow for review of other key data to inform on the objectives of the study while maintaining study integrity and the safety of subjects and site personnel.	[redacted] [redacted] [redacted] [redacted] VX19-445-116 [redacted] [redacted]

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