1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3b Open-label Study Evaluating the Safety of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Cystic Fibrosis Subjects

Vertex Study Number: VX19-445-115

IND Number: [redacted]

EudraCT Number: 2019-003455-11

Date of Protocol: 21 December 2021 (Version 2.2 AU and BE)

Replaces Version 2.1 AU and BE, dated 19 March 2021

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

2 PROTOCOL SYNOPSIS

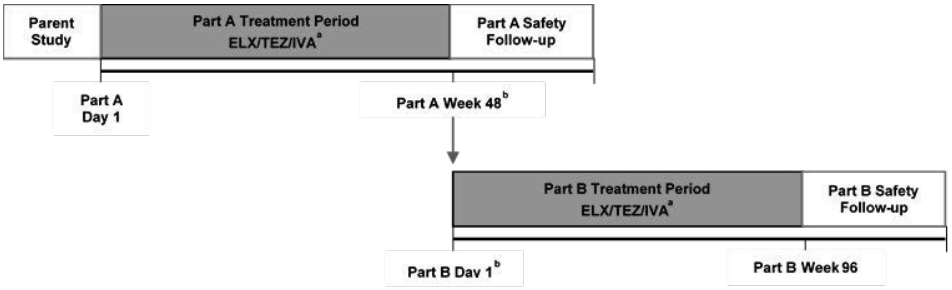
Title	A Phase 3b Open-label Study Evaluating the Safety of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Cystic Fibrosis Subjects
Brief Title	A Study Evaluating the Safety of Elexacaftor Combination Therapy
Clinical Phase and Clinical Study Type	Phase 3b, safety
Objectives	**Primary Objective** To evaluate the safety and tolerability of elexacaftor (VX-445; ELX)/tezacaftor (TEZ)/ivacaftor (IVA)
Endpoints	**Primary Endpoint** Safety and tolerability of ELX/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry
Number of Subjects	Up to approximately 158 subjects are expected to enroll in this open-label study
Study Population	Male and female cystic fibrosis (CF) subjects with an F/F mutation who are 12 years of age or older
Investigational Drug	**Active substance:** ELX **(**VX-445)/TEZ (VX-661)/IVA (VX-770) **Activity:** CFTR correctors (ELX and TEZ) and potentiator (IVA); increased Cl^- secretion **Strength and route of administration:** 100 mg/50 mg/75 mg, oral **Active substance:** IVA (VX-770) **Activity:** CFTR potentiator; increased Cl^- secretion **Strength and route of administration:** 150 mg, oral
Study Duration	For subjects who participate in both Parts A and B, the total study duration is approximately 148 weeks (from the first dose of study drug in this study), including a treatment duration of 144 weeks (Treatment Periods of 48 weeks in Part A and 96 weeks in Part B), and a 4-week Safety Follow-up Visit.

Study Design

This is a Phase 3b, 2-part, multicenter, open-label study for subjects who complete a parent study and meet eligibility criteria. A schematic of the study design is shown in Figure 2-1.

All subjects in Parts A and B will receive the triple combination of ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h. Subjects who complete Part A will have the opportunity to participate in Part B for an additional 96 weeks. For all subjects, a Safety Follow-up Visit is scheduled to occur 28 (± 7) days after the last dose of study drug in Parts A and B.

Figure 2-1 VX19-445-115 Study Design



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

Note: Figure is not drawn to scale.

[a] All subjects will receive ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h.

[b] Subjects whose Part B Day 1 is on the same day or within 1 calendar day as the Part A Week 48 Visit do NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 48 Visit. Subjects whose Part B Day 1 is more than 1 calendar day after Part A Week 48 Visit must complete all assessments specified for the Part A Week 48 AND Part B Day 1 Visits.

For treatment continuity in regions where ELX/TEZ/IVA is not commercially available, an option to return to this study will be offered to subjects who depart this study to enroll in another Vertex study of investigational CFTR modulators (hereafter referred to as "another qualified Vertex study") based on the following:

- Subjects receive open-label ELX/TEZ/IVA during the other study's Run-in Period but have not received study drug in the Treatment Period of the other study, and
- Meet all eligibility criteria for this study at their Returning Visit

Subjects who resume participation in this study will resume treatment with study drug after completion of a Returning Visit. Resumption of participation in this study following departure to another qualified Vertex study will be permitted only once.

Assessments

Safety: AEs, clinical laboratory assessments, ECGs, vital signs, height (for subjects ≤21 years of age on the date of informed consent in a parent study), weight, pulse oximetry, physical examinations (PE), and ophthalmologic examinations (for subjects <18 years of age on the date of informed consent in a parent study).

Statistical Analyses

The safety analyses will be performed for subjects who receive at least 1 dose of study drug in this study. The safety analyses will be descriptive only.

3 SCHEDULE OF ASSESSMENTS

The schedules of assessments for Parts A and B are in Table 3-1 and Table 3-2, respectively. All visits will be scheduled relative to the Part A Day 1 Visit in this study.

Assessments may be performed in any order when more than 1 assessment is required at a particular time point. All assessments should be performed before study drug dosing (Section 9.6.1), unless noted otherwise.

Subjects who depart this study to enroll in another qualified Vertex study, and who meet the eligibility criteria in Section 8, may resume participation in this study only once.

3.1 Part A

Table 3-1 Study VX19-445-115: Part A Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period Part A: Day 1/ Returning Visit[d]	Day 15 (± 3 Days)	Weeks 4, 12, 24, 36 (± 5 Days)	Weeks 8, 16, 20, 28, 32, 40, 44 (± 5 Days)	Week 48 (± 5 Days)[e]	Part A ETT Visit/ Departing Visit[b]	Part A Safety Follow-up Visit (28 ± 7 Days After Last Dose)[c]	Comments
Clinic visit	X	X	X		X	X	X	
Telephone contact				X				Results of a home urine pregnancy test will be reported to the site by telephone (Section 11.2.2)
ICF and assent (when applicable)	X							ICF and assent are not required for Returning Visit
Inclusion and exclusion criteria confirmation	X							Section 8
Height and weight	X		X		X		X	Measured with shoes off. For subjects whose date of informed consent occurs after their 21st birthday, height will not be collected (Section 11.2.4).

[a] All assessments should be performed before study drug dosing, unless noted otherwise.

[b] If the subject prematurely discontinues study drug treatment, an ETT Visit should be scheduled as soon as possible after the decision to discontinue treatment (Section 9.1.3). If the subject prematurely discontinues treatment to participate in another qualified Vertex study, the Departing Visit should be completed before or on the same day as the visit at which they receive the first dose of study drug in the Run-in Period of the other qualified Vertex study. The Safety Follow-up Visit will not be required if the subject enrolls in the other qualified Vertex study within 28 days of the last dose of study drug in this study.

[c] The Safety Follow-up Visit is required for all subjects, unless otherwise specified (Section 9.1.2). For subjects who complete an ETT Visit 3 weeks or later following the last dose of study drug, the ETT Visit will replace the Safety Follow-up Visit.

[d] The Day 1 Visit should occur on the same day as the last scheduled visit in the Treatment Period of a parent study (Section 9.1.1). Assessments at the Day 1 Visit must be performed before study drug dosing. Subjects who resume participation in this study after participation in another qualified Vertex study will complete the Returning Visit (which will consist of all assessments in the Day 1 Visit) and will resume treatment with ELX/TEZ/IVA after completion of the Returning Visit. Study visit numbering for returning subjects will resume based on the last study visit before the Departing Visit in this study. If the Returning Visit window coincides with a scheduled visit in this study, only the Returning Visit assessments will be completed. Subjects who resume participation but have their first dose of study drug in this study delayed will repeat the safety assessments specified to be performed at the Returning Visit before receiving their first dose of study drug.

[e] Subjects whose Part B Day 1 is on the same day or within 1 calendar day as the Part A Week 48 Visit do NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 48 Visit. Subjects whose Part B Day 1 is more than 1 calendar day after Part A Week 48 Visit must complete all assessments specified for the Part A Week 48 AND Part B Day 1 Visits.

Table 3-1 Study VX19-445-115: Part A Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period Part A					Part A ETT Visit/ Departing Visit[b]	Part A Safety Follow-up Visit (28 ± 7 Days After Last Dose)[c]	Comments
	Day 1/ Returning Visit[d]	Day 15 (± 3 Days)	Weeks 4, 12, 24, 36 (± 5 Days)	Weeks 8, 16, 20, 28, 32, 40, 44 (± 5 Days)	Week 48 (± 5 Days)[e]			
Ophthalmologic examination					X	X		Subjects <18 years of age on the date of informed consent in a parent study and have completed at least 12 weeks of study drug treatment since their last ophthalmologic examination will have an ophthalmologic examination at the Part A Week 48 Visit or the Part A ETT Visit/ Departing Visit, whichever comes first. See Section 11.2.7 for acceptable assessment windows.
Complete physical examination (PE)	X				X	X		Symptom-directed PEs may be performed at any time if deemed necessary by the investigator (Section 11.2.3)
Pregnancy test	Urine		Urine	Urine	Serum	Serum	Serum	For all female subjects, at telephone contacts, a urine pregnancy test will be performed with a home kit provided by the study site. Results of the home pregnancy test will be reported to the site by telephone (Section 11.2.2).
Standard 12-lead ECG	X	X	Weeks 12, 24		X	X	X	Performed after subject has been at rest for at least 5 minutes (Sections 11.2.3, 11.2.5, and 11.2.6)
Vital signs	X	X	X		X	X	X	
Pulse oximetry	X	X	X		X	X	X	
Urinalysis	X				X	X	X	Section 11.2.2
Hematology	X	X	X		X	X	X	
Coagulation	X		Week 24		X	X	X	
Serum chemistry	X	X	X		X	X	X	
Study drug count	X	X	X		X	X		

Table 3-1 Study VX19-445-115: Part A Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period Part A					Part A ETT Visit/ Departing Visit[b]	Part A Safety Follow-up Visit (28 ± 7 Days After Last Dose)[c]	Comments
	Day 1/ Returning Visit[d]	Day 15 (± 3 Days)	Weeks 4, 12, 24, 36 (± 5 Days)	Weeks 8, 16, 20, 28, 32, 40, 44 (± 5 Days)	Week 48 (± 5 Days)[e]			
Study drug dosing	Day 1 through evening before Part A Week 48 Visit							Subjects on study drug interruption from a parent study or another qualified Vertex study may NOT begin dosing until they meet the resumption criteria in Section 9.8. The last dose of Part A should be taken on the evening before the Week 48 Visit. Refer to Section 9.6.1 for study drug administration details.
Medications review	Continuous from signing of the ICF through completion of study participation							Completion of study participation is defined in Section 9.1.5.
Treatments and procedures review	Continuous from signing of the ICF through completion of study participation							
AEs and SAEs	Continuous from signing of the ICF through completion of study participation							Completion of study participation is defined in Section 9.1.5. Refer to Section 13.1 for reporting and documentation of SAEs.

AE: adverse event; ETT: early termination of treatment; ICF: informed consent form; PE: physical examination; SAE: serious adverse event

3.2 Part B

Table 3-2 Study VX19-445-115: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period Part B: Day 1/ Returning Visit[d]	Treatment Period Part B: Weeks 12, 24, 36, 48, 60, 72, 84 (± 5 Days)	Treatment Period Part B: Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92 (± 5 Days)	Treatment Period Part B: Week 96 (± 5 Days)	Part B ETT Visit/ Departing Visit[b]	Part B Safety Follow-up Visit (28 ± 7 Days After Last Dose)[c]	Comments
Clinic visit	X	X		X	X	X	
Telephone contact			X				Results of a home urine pregnancy test will be reported to the site by telephone (Section 11.2.2)
Part B ICF and assent (when applicable)	X						ICF and assent are not required for Returning Visit
Inclusion and exclusion criteria confirmation	X						Section 8
Height and weight	X	X		X		X	Measured with shoes off. For subjects whose date of informed consent occurs after their 21st birthday, height will not be collected (Section 11.2.4).

[a] All assessments should be performed before study drug dosing, unless noted otherwise.

[b] If the subject prematurely discontinues study drug treatment, an ETT Visit should be scheduled as soon as possible after the decision to discontinue treatment (Section 9.1.3). If the subject prematurely discontinues treatment to participate in another qualified Vertex study, the Departing Visit should be completed before or on the same day as the visit at which they receive the first dose of study drug in the Run-in Period of the other qualified Vertex study. The Safety Follow-up Visit will not be required if the subject enrolls in the other qualified Vertex study within 28 days of the last dose of study drug in this study.

[c] The Safety Follow-up Visit is required for all subjects, unless otherwise specified. For subjects who complete an ETT Visit 3 weeks or later following the last dose of study drug, the ETT Visit will replace the Safety Follow-up Visit (Section 9.1.2).

[d] Subjects whose Part B Day 1 is on the same day or within 1 calendar day of the Part A Week 48 Visit do NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 48 Visit. Subjects whose Part B Day 1 is more than 1 calendar day after the Part A Week 48 Visit must complete all assessments specified for the Part A Week 48 AND Part B Day 1 Visits. Subjects who resume participation in this study after participation in another qualified Vertex study will complete the Returning Visit (which will consist of all assessments in the Day 1 Visit) and will resume treatment with ELX/TEZ/IVA after completion of the Returning Visit. Study visit numbering for returning subjects will resume based on the last study visit before the Departing Visit in this study. If the Returning Visit window coincides with a scheduled visit in this study, only the Returning Visit assessments will be completed. Subjects who resume participation but have their first dose of study drug in this study delayed will repeat the safety assessments specified to be performed at the Returning Visit before receiving their first dose of study drug.

Table 3-2 Study VX19-445-115: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period Part B: Day 1/ Returning Visit[d]	Treatment Period Part B: Weeks 12, 24, 36, 48, 60, 72, 84 (± 5 Days)	Treatment Period Part B: Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92 (± 5 Days)	Treatment Period Part B: Week 96 (± 5 Days)	Part B ETT Visit/ Departing Visit[b]	Part B Safety Follow-up Visit (28 ± 7 Days After Last Dose)[c]	Comments
Ophthalmologic examination				X	X		Subjects <18 years of age on the date of informed consent in a parent study and who have completed at least 12 weeks of study drug treatment since their last ophthalmologic examination will have an ophthalmologic examination at the Part B Week 96 Visit or the Part B ETT Visit/Departing Visit, whichever comes first. See Section 11.2.7 for acceptable assessment windows.
Complete physical examination (PE)	X			X	X		Symptom-directed PEs may be performed at any time if deemed necessary by the investigator (Section 11.2.3)
Pregnancy test	Urine	Urine	Urine	Serum	Serum	Serum	For all female subjects, at telephone contacts, a urine pregnancy test will be performed with a home kit provided by the study site. Results of the home pregnancy test will be reported to the site by telephone (Section 11.2.2).
Standard 12-lead ECG	X	Week 24, 48		X	X	X	Performed after subject has been at rest for at least 5 minutes (Sections 11.2.3, 11.2.5, and 11.2.6)
Vital signs	X	X		X	X	X	
Pulse oximetry	X	X		X	X	X	
Urinalysis	X			X	X	X	Section 11.2.2
Hematology	X	X		X	X	X	
Coagulation	X	Week 48		X	X	X	
Serum chemistry	X	X		X	X	X	
Study drug count	X	X		X	X		

Table 3-2 Study VX19-445-115: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period Part B: Day 1/ Returning Visit[d]	Treatment Period Part B: Weeks 12, 24, 36, 48, 60, 72, 84 (± 5 Days)	Treatment Period Part B: Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92 (± 5 Days)	Treatment Period Part B: Week 96 (± 5 Days)	Part B ETT Visit/ Departing Visit[b]	Part B Safety Follow-up Visit (28 ± 7 Days After Last Dose)[c]	Comments
Study drug dosing	Day 1 through evening before Part B Week 96 Visit						Subjects on study drug interruption from Part A or another qualified Vertex study may NOT begin dosing in Part B until they meet the resumption criteria in Section 9.8. The first dose of Part B will be given at the Day 1 Visit. Refer to Section 9.6.1 for study drug administration details.
Medications review	Continuous from signing of the Part B ICF through completion of study participation						Completion of study participation is defined in Section 9.1.5.
Treatments and procedures review	Continuous from signing of the Part B ICF through completion of study participation						
AEs and SAEs	Continuous from signing of the Part B ICF through completion of study participation						Completion of study participation is defined in Section 9.1.5. Refer to Section 13.1 for reporting and documentation of SAEs.

AE: adverse event; ETT: early termination of treatment; ICF: informed consent form; PE: physical examination; SAE: serious adverse event

4 TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BMI	body mass index
CF	cystic fibrosis
CFTR	CF transmembrane conductance regulator protein
CFTR	CF transmembrane conductance regulator gene
Cl^-	chloride ion
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
EDC	electronic data capture
ELX	elexacaftor
ETT	Early Termination of Treatment
EU	European Union
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 on the wild-type protein
F508del	CFTR protein lacking the phenylalanine normally found at position 508 of the wild-type protein
FDA	Food and Drug Administration
FDC	fixed-dose combination
F/F	homozygous for *F508del*
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GPS	Global Patient Safety
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IPD	important protocol deviation
IRB	institutional review board
IVA	ivacaftor
LUM	lumacaftor
max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function
min	minimum value
PE	physical examination
P-gp	P-glycoprotein
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PR	PR interval, segment

Abbreviation	Definition
PT	Preferred Term
q12h	every 12 hours
qd	once daily
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
RR	interval from the onset of 1 QRS complex to the next
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SUSAR	suspected, unexpected, serious adverse reaction
SI	SI units (International System of Units)
SOC	System Organ Class
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
ULN	upper limit of normal
US	United States
USA	United States of America

5 INTRODUCTION

5.1 Background

Cystic fibrosis (CF) is an autosomal recessive chronic disease with serious morbidities and frequent premature mortality. CF affects more than 70,000 individuals worldwide[1] (approximately 30,000 in the US[2] and 45,000 in the EU[3]). Based on its prevalence, CF qualifies as an orphan disease.[4, 5]

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

The most common disease-causing *CFTR* mutation is *F508del*, which accounts for approximately 70% of the identified alleles in people with CF.[10] Approximately 40% to 45% of people with CF are homozygous for *F508del* (F/F), and approximately 85% have at least one *F508del* allele. [2, 3]

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

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

Elexacaftor (VX-445; ELX) is a next-generation CFTR corrector. In vitro, the triple combination 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 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 TEZ, IVA, and TEZ/IVA (F/MF genotypes); and those homozygous for *F508del* (F/F genotypes).

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

5.2 Study Rationale

This study will evaluate the safety of up to 144 weeks of treatment with ELX/TEZ/IVA in subjects with CF who have an F/F genotype who complete a parent study (Study VX18-445-109). The potential for benefit in these patients is supported by published

Phase 2 and publicly disclosed Phase 3 clinical data in subjects with F/F genotypes. In addition, ELX/TEZ/IVA is generally safe and well tolerated (refer to ELX Investigator's Brochure).

Data from this study are intended to enrich the body of evidence showing that ELX/TEZ/IVA is safe and well tolerated in subjects with F/F genotypes.

6 STUDY OBJECTIVES

6.1 Primary Objective

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

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Safety and tolerability of treatment with ELX/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry

8 STUDY POPULATION

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

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

8.1 Inclusion Criteria

1. Subject (or his or her legally appointed and authorized representative) will sign and date an informed consent form (ICF), and, when appropriate, an assent form.
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Did not withdraw consent from a parent study and (if continuing on to Part B of this study) did not withdraw consent in Part A.
4. For each part of the study, meets the following criteria:
    - For subjects entering Part A of this study:
        - Completed study drug treatment in a parent study, or
        - Had study drug interruptions(s) in a parent study, but did not permanently discontinue study drug, and completed study visits up to the last scheduled visit of the Treatment Period of a parent study.
    - For subjects continuing on to Part B of this study:
        - Completed study drug treatment in Part A, or
        - Had study drug interruptions(s) in Part A, but did not permanently discontinue study drug, and completed study visits up to the last scheduled visit of the Treatment Period of Part A.

- For subjects being considered for resumption of participation in this study after enrolling in another qualified Vertex study:
  - Completed the ETT visit in another qualified Vertex study before or on the same day as the Returning Visit in this study. If more than 30 days have elapsed since the ETT visit in the other qualified Vertex study, approval of the medical monitor is required, and
  - Did not depart this study more than once to participate in another qualified Vertex study.

8.2 Exclusion Criteria

1. History of any comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.
2. Pregnant and breast-feeding females. Female subjects must have a negative pregnancy test at the Part A Day 1 and Part B Day 1 Visits before receiving the first dose of study drug in each Part.
3. History of drug intolerance in a parent study or in the current study that would pose an additional risk to the subject in the opinion of the investigator (e.g., subjects with a history of allergy or hypersensitivity to the study drug).
4. Current participation in an investigational drug trial other than a parent study or the current study. Participation in a noninterventional study (including observational studies, registry studies, and studies requiring blood collections without administration of study drug) and screening for another Vertex study is permitted.
5. For subjects being considered for resumption of participation in this study after enrolling in another qualified Vertex study, the following exclusion criteria also apply:
   - Subject received the first dose of study drug in the Treatment Period of another qualified Vertex study, or
   - Subject has access to commercially available or managed-access-program-supplied ELX/TEZ/IVA.

9 STUDY IMPLEMENTATION

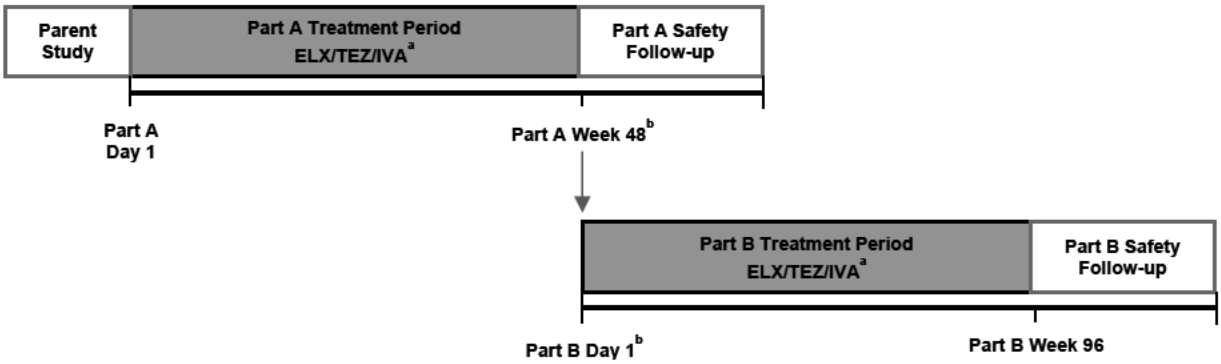
9.1 Study Design

This is a Phase 3b, 2-part, multicenter, open-label study for subjects who complete a parent study (Study VX18-445-109; a Phase 3b study evaluating ELX/TEZ/IVA) and meet eligibility criteria (Section 8). A schematic of the study design is shown in Figure 9-1.

All subjects in Parts A and B will receive the triple combination of ELX 200 mg once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) (the same dose level as that evaluated in the Phase 3 program of ELX/TEZ/IVA). Study drug administration is described in Section 9.6.1. Subjects who complete Part A will have the opportunity to participate in Part B for an additional 96 weeks.

Study visits and assessments for Parts A and B are shown in Table 3-1 and Table 3-2, respectively. All visits will occur within the windows specified.

Figure 9-1 VX19-445-115 Study Design



ELX: elexacaftor; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor
Note: Figure is not drawn to scale.

[a] All subjects will receive ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h.

[b] Subjects whose Part B Day 1 is on the same day or within 1 calendar day of the Part A Week 48 Visit do NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 48 Visit. Subjects whose Part B Day 1 is more than 1 calendar day after Part A Week 48 Visit must complete all assessments specified for the Part A Week 48 AND Part B Day 1 Visits.

For treatment continuity in regions where ELX/TEZ/IVA is not commercially available, an option to return to this study will be offered to subjects who depart this study to enroll in another Vertex study of investigational CFTR modulators (referred to as "another qualified Vertex study") based on the following:

- Subjects have received open-label ELX/TEZ/IVA during the other study's Run-in Period but have not received study drug in the Treatment Period of the other study, and
- Meet all eligibility criteria for this study (Section 8) at their Returning Visit.

Subjects who resume participation in this study will resume treatment with study drug after completion of a Returning Visit. Resumption of participation in this study following departure to another qualified Vertex study will be permitted only once.

9.1.1 Treatment Period

Treatment Period assessments for Parts A and B are listed in Table 3-1 and Table 3-2, respectively. Study drug administration details are provided in Section 9.6.

Part A

Subjects will receive the first dose of study drug on Part A Day 1 after obtaining informed consent (and assent, when applicable) and confirming eligibility. Subjects who enroll in this study on a study drug interruption will NOT receive the first dose of study drug until they meet the resumption criteria in Section 9.8; before receiving study drug, subjects will repeat all Part A Day 1 assessments.

The Part A Day 1 Visit of this study should be on the same day as the last scheduled visit in the Treatment Period of a parent study.

Subjects whose Part A Day 1 Visit is NOT within 1 day of the last scheduled visit in the Treatment Period of a parent study will have all Part A Day 1 assessments performed.

Subjects whose Part A Day 1 Visit is within 1 day of the last scheduled visit in the Treatment Period of a parent study will NOT have to repeat assessments that were performed as part of the last scheduled visit in a parent study Treatment Period.

Part B

For subjects who elect to participate in Part B, the Part A Week 48 Visit will be the start of treatment in Part B (i.e., Part B Day 1).

Subjects whose Part B Day 1 is on the same day or within 1 calendar day of the Part A Week 48 Visit do NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 48 Visit. Subjects whose Part B Day 1 is more than 1 calendar day after Part A Week 48 Visit must complete all assessments specified for the Part A Week 48 AND Part B Day 1 Visits.

Subjects Resuming Participation After Discontinuation From Another Qualified Vertex Study

Subjects who resume participation in this study will complete the Returning Visit and resume treatment with ELX/TEZ/IVA after completion of the Returning Visit. Study visit numbering for returning subjects will resume based on the last study visit before the Departing Visit in this study. If the subject's Returning Visit window coincides with a scheduled study visit in this study, only the Returning Visit assessments will be completed, after which subjects will resume study visits in this study.

Subjects who resume participation but have their first dose of study drug in this study delayed will repeat the safety assessments specified to be performed at the Returning Visit before receiving their first dose of study drug (see Section 3).

The Early Termination of Treatment (ETT) Visit in another qualified Vertex study and the Returning Visit in this study may occur on the same day. If completed on the same day or within 1 calendar day, any assessments completed at the ETT in the other qualified Vertex study do not have to be repeated at the Returning Visit in this study.

9.1.2 Safety Follow-up

The Safety Follow-up Visit is scheduled to occur 28 (± 7) days after the last dose of study drug in Parts A and B. The Safety Follow-up Visit assessments are listed in Table 3-1 and Table 3-2, respectively.

The Safety Follow-up Visit is required for all subjects. However, subjects in Parts A and B who transition within 28 days of the last dose of study drug to either:

- a commercially available Vertex CFTR modulator regimen
- managed access program-supplied Vertex CFTR modulator regimen
- or, to another Part of the current study or another qualified Vertex study

will complete the respective Part A Week 48 or Part B Week 96 Visit. If the transition occurs before the Part A Week 48 Visit or Part B Week 96 Visit, then subjects will complete the Early Termination of Treatment (ETT) Visit. In these cases, the Part A Week 48/Part B Week 96 Visit or the ETT Visit, whichever is applicable, will replace the Safety Follow-up Visit.

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

9.1.3 Early Termination of Treatment

Departing Visit

If a subject enrolls in another qualified Vertex study, the Departing Visit should be completed before or on the same day as the visit at which they receive the first dose of study drug in the Run-in Period of the other qualified Vertex study. If completed on the same day, the Schedule of Assessments in the other qualified Vertex study should be followed and study assessments in this study that were specified to be performed in the other qualified Vertex study do not have to be repeated. If the subject does not resume participation in this study, they will not be required to complete a separate ETT visit.

ETT Visit

If a subject prematurely discontinues study drug treatment for any reason other than to enroll in another qualified Vertex study, an ETT Visit should be scheduled as soon as possible after the decision to discontinue treatment.

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

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

9.1.4 Lost to Follow-up

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

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

9.1.5 Completion of Study Participation

Completion of study participation for each individual subject is defined as: the Safety Follow-up Visit; or, in situations in which the ETT Visit or the Part A Week 48 or Part B Week 96 Visit replaces the Safety Follow-up Visit (Section 9.1.2), the ETT Visit or the Part A Week 48 or Part B Week 96 Visit.

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

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

The end of study is defined in Section 13.2.8.

9.2 Method of Assigning Subjects to Treatment Groups

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

9.3 Rationale for Study Elements

9.3.1 Study Design and Population

Subjects who completed treatment in a parent study (Study VX18-445-109) and met eligibility criteria will be able enroll in Part A of this study, which is designed to provide long-term safety data in CF subjects, homozygous for *F508del* (F/F), 12 years of age or older, treated with ELX/TEZ/IVA.

9.3.2 Study Drug Dose and Duration

All subjects in Parts A and B of the study will receive ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h (the same dosage as that used in the ELX Phase 3 program). This dose was demonstrated to be generally safe and efficacious in Phase 3 studies of ELX/TEZ/IVA.

The overall treatment duration will be up to 144 weeks, which is considered sufficient for the evaluation of the safety of treatment with ELX/TEZ/IVA.

9.3.3 Rationale for Study Assessments

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

9.4 Study Restrictions

Table 9-1 lists prohibited medications. A non-exhaustive list of study prohibitions and cautions for medication will be provided in the Study Reference Manual. Guidance for concomitant medications is provided in Section 9.5.

Table 9-1 Prohibited Medications

Medication	Timing of Restriction: Start of Restriction	Timing of Restriction: End of Restriction	Rationale
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of study drug on Part A 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 of CYP3A and moderate and strong 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 study drug on Part A Day 1	None allowed through completion of study participation	
CFTR modulators (investigational or approved), except for study drugs in a parent study and this study	None allowed from the first dose of study drug on Part A Day 1	None allowed through completion of study participation	These agents may confound the results of this study.

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

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

9.5 Prior and Concomitant Medications

Information regarding prior and concomitant medications, including CF medications, other medications, and herbal and naturopathic remedies, will be collected from each subject's source documentation for medications taken within 56 days before the first dose of study drug in this study through completion of study participation, as defined in Section 9.1.5. For subjects who enroll in another qualified Vertex study and resume participation in this study, any new medications started after the subject first departs this study will be collected for the period after the Departing Visit and before study drug dosing resumes in this study, through completion of study participation.

- 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.

9.6 Administration

9.6.1 Dosing

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

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

- It is recommended that the dose be taken within 30 minutes of the start of the meal or snack.
- Study drug will be administered as fixed-dose combination (FDC) tablet(s) (e.g., 2 ELX/TEZ/IVA) in the morning and as 1 IVA tablet in the evening. For each subject, doses of study drugs should be taken at approximately the same time (± 2 hours) each day.
- On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. A meal or snack will be provided by the site for the morning dose of study drug.
- If a subject's scheduled visit is to occur in the afternoon, the following guidelines should be used:
    - If the dose in the clinic will be within 6 hours of the subject's scheduled morning dose, the subject should withhold their morning dose of study drug and the morning dose will be administered in the clinic.
    - If the dose in the clinic will be more than 6 hours after the subject's scheduled morning dose, the subject should take the morning dose of study drug at home.

Subjects will be instructed to bring all used and unused materials associated with the study drug to the site; study drug will be dispensed at each visit, as appropriate.

9.6.2 Missed Doses

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

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

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

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

9.7 Dose Modification for Toxicity

No dose modifications for toxicity are allowed. Treatment may be interrupted; if any unacceptable toxicity arises, individual subjects will discontinue dosing.

9.8 Study Drug Interruption and Stopping Rules

In subjects who have interrupted study drug for >72 hours for any reason, the investigator should resume study drug only after a thorough investigation of the cause for interruption. The investigator will evaluate the subject's clinical stability and should consider resumption of study

drug only after the subject is clinically stable and there is no comorbidity or condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.

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

9.8.1 Liver Function Tests

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

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

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

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

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

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

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

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

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

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

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

to baseline 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 their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. A subject who withdraws from study drug treatment will continue to be followed unless the subject withdraws consent or assent.

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

- Meets any of the stopping (discontinuation) criteria (Section 9.8)
- Becomes pregnant (Section 11.2.8.2)

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for an ETT Visit and Safety Follow-up Visit, if applicable (see Section 9.1.3), 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 compound, for other drugs and diagnostics, in publications and presentations, and for education purposes. If the subject withdraws from the study, the study data and samples collected will remain part of the study. A subject will not be able to request the withdrawal of his/her information from the study data. A subject may request destruction of the samples collected from him/her during the study as long as those samples can be identified as his/her samples.

9.10 Replacement of Subjects

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

10 STUDY DRUG INFORMATION AND MANAGEMENT

10.1 Preparation and Dispensing

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

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

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

IVA will be supplied as a film-coated tablet containing 150 mg IVA (Table 10-1).

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

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

Drug Name, Dosing Form, Route	Strength
ELX/TEZ/IVA, FDC tablet, oral	
ELX	100 mg
TEZ	50 mg
IVA	75 mg
IVA, tablet, oral	150 mg

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

10.4 Drug Accountability

The pharmacist or designated study site staff will maintain information 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 is an open-label study.

11 ASSESSMENTS

The schedule of assessments for Parts A and B are shown in Table 3-1 and Table 3-2, respectively.

11.1 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, and weight. Select demographic and baseline characteristic data and medical history will be derived from a parent study.

11.2 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, physical examinations (PEs), and pulse oximetry.

For subjects <18 years of age on the date of informed consent in a parent study, ophthalmological examinations will be performed as specified for Parts A and B in Table 3-1 and Table 3-2, respectively.

11.2.1 Adverse Events

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

11.2.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory, with the exception of the urine pregnancy tests. As described below, urine pregnancy tests will either be analyzed by the site or at home using a home pregnancy test kit. On Part A Day 1 and Part B Day 1 (and the Returning Visit if applicable), blood samples will be collected before the first dose of the study drug.

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

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

Table 11-1 Safety Laboratory Test Panels

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

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

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

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

Pregnancy (beta-human chorionic gonadotropin) Tests for female subjects: 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 pregnancy test kit provided by the site. Results will be reported to the site by telephone. The urine pregnancy test on Part A Day 1 and on Part B Day 1 (and the Returning Visit if applicable) must be negative before the first dose of study drug. Additional pregnancy tests may be required according to local regulations and/or requirements.

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

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

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

11.2.3 Physical Examinations and Vital Signs

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

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

Vital signs include blood pressure (systolic and diastolic), temperature, pulse rate, and respiration rate. These will be assessed before dosing and following at least a 5-minute rest. A consistent methodology should be used for repeat measurements of these parameters at a clinical site.

11.2.4 Height and Weight

Height and weight will be measured with shoes off, as applicable.

- Height will not be collected for subjects whose date of informed consent in Part A occurs after their 21st birthday.
- Height will be collected through the first visit after the subject's 21st birthday for subjects whose date of informed consent in Part A occurs on or before their 21st birthday; height will not be collected at subsequent visits.

11.2.5 Pulse Oximetry

Pulse oximetry is a noninvasive measure of oxygen delivery to the tissues and has been correlated with clinical status and lung function. Arterial oxygen saturation by pulse oximetry will be assessed following at least a 5-minute rest and before study drug dosing.

11.2.6 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.

Subjects will be instructed to rest for at least 5 minutes before having an ECG performed.

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

To ensure the 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. Further details pertaining to ECGs will be provided to sites in the ECG Manual.

11.2.7 Ophthalmologic Examination

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

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

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

An ophthalmologic examination should occur within 4 weeks before the Part A Week 48 Visit for those subjects completing Part A. For subjects continuing on to Part B, an ophthalmologic examination should occur within 4 weeks before the Part B Week 96 Visit. In both Parts A and B, this examination should be completed within 4 weeks before the Part A Week 48 Visit or the Part B Week 96 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 for Parts A and B in Table 3-1 and Table 3-2, respectively.

Subjects <18 years of age on the date of informed consent in a parent study and who have completed at least 12 weeks of study drug treatment since their last ophthalmologic examination will have an ophthalmologic examination at either the Part A Week 48/Part B Week 96 Visit or the ETT Visit, whichever comes first, in both Parts A and B as applicable, except for those subjects who have withdrawn consent or assent.

Any clinically significant abnormal findings will be reported as AEs.

11.2.8 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.

11.2.8.1 Contraception

Contraception requirement for a couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. True

abstinence must be practiced from the Part A Day 1 Visit through 90 days after the last dose of study drug.

- If the male is infertile (e.g., bilateral orchiectomy). If a male subject is assumed to have complete bilateral absence of the vas deferens, infertility must be documented before the first dose of study drug (e.g., examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound).
- If the female is of non-childbearing potential. To be considered of non-childbearing potential, the female must meet at least 1 of the following criteria:
  - Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum 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 as a couple. Acceptable methods of contraception must be used as specified (Table 11-2) from signing of consent, before the first dose of study drug, 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.

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 post-vasectomy semen analysis for sperm	Yes	Yes
Bilateral tubal occlusion (e.g., ligation) performed at least 6 months previously	Yes	Yes
Male or female condom with or without spermicide[a]	Yes	Yes
Female barrier contraception (such as diaphragm, cervical cap, or sponge) with spermicide	Yes	Yes
Continuous use of an intrauterine device for at least 90 days before the first dose of study drug		
Hormone-releasing	Yes	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.
- For male subjects with a female partner of childbearing potential, the couple should not plan to become pregnant during the study or within 90 days after the last dose of study drug, with the exception of couples who plan to become pregnant by artificial insemination using sperm banked by the male subject before the first dose of study drug or sperm from another source.

11.2.8.2 Pregnancy

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

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

The subject or partner will be followed until the end of the pregnancy and the infant will be followed for 1 year after the birth, provided informed consent (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

12.1 Sample Size

The primary objective of the study is the evaluation of the safety and tolerability of ELX/TEZ/IVA. This is an open-label extension study that will enroll subjects who did not discontinue study drug during the Treatment Period in a parent study and meet eligibility criteria in this study.

Up to approximately 158 subjects are expected to enroll in this open-label extension study.

12.2 Analysis Sets

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

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

12.3 Statistical Analysis

12.3.1 General Considerations

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

Categorical variables will be summarized using counts and percentages.

Baseline value, unless otherwise specified, for the safety analysis will be the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of ELX/TEZ/IVA either in a parent study or this study, as applicable. For assessments collected in duplicate or triplicate, the baseline value will be defined as the average of non-missing values.

Change (absolute change) from baseline will be calculated as Post-baseline value − Baseline value.

Treatment-emergent (TE) Period will include the time period starting from the date of the first dose of study drug in Part A or Part B of this open-label study to 28 days after the last dose of the study drug in Part A or Part B, or to the completion date of study participation (as defined in Section 9.1.5), whichever occurs first. For subjects who enroll in another qualified Vertex study before completing this study and resume participation in this study, the TE Period will exclude the time spent in the other study.

Additional details of the analysis will be specified in the statistical analysis plan (SAP).

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

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

- All Subjects Set
- Safety Set
- Completed treatment
- Prematurely discontinued treatment and the reasons for discontinuation
- Completed study
- Prematurely discontinued the study and the reasons for discontinuation
- Departed this study to enroll in another qualified Vertex study

- Departed this study to enroll in another qualified Vertex study and returned to this study

12.3.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by descriptive summary statistics. Demographics and baseline characteristics will be obtained from the parent study baseline.

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

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

12.3.2.3 Prior and Concomitant Medications

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

- **Prior medication:** any medication that was administered within the 56 days before the first dose of study drug in this open-label study. For subjects who enroll in another qualified Vertex study and resume participation in this study, any new or changed medication administered after the Departing Visit and prior to the first dose of study drug after resuming participation in this study will also be considered prior medication.
- **Concomitant medication:** medication continued or newly received during the TE Period in this open-label study.
- **Post-treatment medication:** medication continued or newly received after the TE Period in this open-label study.

A given medication may be classified as a prior medication, a concomitant medication, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment. If a medication has a missing or partially missing start/end date or time and if it cannot be determined whether it was taken before initial dosing, concomitantly during the TE Period, or beyond 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 Safety Set. Post-treatment medications will be provided separately in an individual subject data listing.

12.3.2.4 Study Drug Exposure and Compliance

Study drug exposure will be summarized based on the Safety Set, defined as the last day of study drug minus the first day of study drug plus 1, regardless of study drug interruption. For subjects who enroll in another qualified Vertex study and resume participation in this study, time spent in the other study will be excluded.

Study drug compliance will be summarized based on the Safety Set, and will be calculated as: $100 \times [1 - (\text{total number of days of study drug interruption in this open-label study}) / (\text{duration of study drug exposure in days in this open-label study})]$. A study drug interruption on a given day is defined as an interruption of any study drug on that day. For subjects who enroll in another

qualified Vertex study and resume participation in this study, time spent in the other study will be excluded.

12.3.2.5 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

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

12.3.3 Efficacy Analysis

Not applicable

12.3.4 Safety Analysis

All safety analyses will be based on the TE Period in this open-label study for subjects in the Safety Set, unless otherwise specified.

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

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

All safety data will be presented in individual subject data listings. Only descriptive analyses of safety data 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 since the end of the TE Period in a parent study and before the first dose of ELX/TEZ/IVA in the TE Period in this open-label study. For subjects who depart this study to enroll in another qualified Vertex study and resume participation in this study, details of pre-treatment AEs will be specified in the SAP.
- **TEAE**: any AE that worsened (either in severity or seriousness) or newly developed at or after the first dose date of ELX/TEZ/IVA in the TE Period in this open-label study.
- **Post-treatment AE:** any AE that worsened (either in severity or seriousness) or newly developed after the TE Period in this open-label study.

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

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

- Overview of TEAEs

- TEAEs
- Related TEAEs
- TEAEs by maximum severity
- Grade 3/4 TEAEs
- Serious TEAEs
- Related serious TEAEs
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption

Summaries will be presented by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once, only the maximum severity level will be presented in the severity summaries, and the strongest relationship level 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 TE laboratory measurements, the observed values and change from baseline values of the continuous laboratory parameters will be summarized in SI units at each time point during the TE Period.

For threshold analysis, the number and percentage of subjects with at least 1 event during the TE Period will be summarized. 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 laboratory assessment values will be provided. This listing will include data from scheduled and unscheduled time points.

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

12.3.4.3 Electrocardiogram

For the TE ECG measurements, a summary of observed values and change from baseline values will be provided at each time point during the TE Period, for the following ECG interval measurements (in msec): RR, PR, QT, QT corrected for heart rate (HR) intervals (QTcF), QRS duration, and HR (beats per minute).

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

Additional ECG analyses may be described in the SAP.

12.3.4.4 Vital Signs

For the TE vital signs measurements, the observed values and change from baseline values will be summarized at each time point during the TE Period in this open-label study. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute).

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

Additional vital signs analyses may be described in the SAP.

12.3.4.5 Pulse Oximetry

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

12.3.5 Independent Data Monitoring Committee Analyses

12.3.5.1 IDMC Analysis

Not applicable.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

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

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

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

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

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

13.1.1.3 Documentation of Adverse Events

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

- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, the earliest of
  - 28 days after the last dose of study drug, or
  - the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (see Section 9.1.3).
- For subjects who depart this study to enroll in another qualified Vertex study: through the time of enrollment in another qualified Vertex study

For subjects who depart this study to enroll in another qualified Vertex study and resume participation in this study, AEs will be collected from the time of the Returning Visit until the subject completes study participation in this study. AEs that fully occur (start and end) in the other qualified Vertex study will be recorded as medical history; AEs that started during participation in the other qualified Vertex study and are ongoing at the time of the Returning Visit in this study will be recorded as AEs in this study.

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: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed July 2018). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." When considering the severity of an AE in a pediatric subject, the investigator will consider that reference ranges for pediatric clinical laboratory parameters may differ from those in the CTCAE. The severity of an AE described by a term that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

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

AE: adverse event

13.1.1.5 Adverse Event Causality

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

Table 13-2 Classifications for AE Causality

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

AE: adverse event

13.1.1.6 Study Drug Action Taken

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

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

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

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

13.1.1.7 Adverse Event Outcome

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

Table 13-4 Classifications for Outcome of an AE

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

AE: adverse event

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

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

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

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

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

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

13.1.2.2 Reporting and Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent 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 subjects who depart this study to participate in another qualified Vertex study, SAEs will be collected in the same manner as described for AEs (Section 13.1.1.3).

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

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted]

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

13.2.2 Subject Information and Informed Consent

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

13.2.3 Investigator Compliance

No modifications to the protocol will be made without the approval of both the investigator and Vertex. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study 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 data provided to Vertex, 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 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.

13.2.6 Record Retention

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

13.2.7 Study Termination

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

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

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

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

13.2.8 End of Study

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

13.3 Data Quality Assurance

Vertex or its designated representative will conduct a study site visit to verify the qualifications of each investigator, inspect clinical study site facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation. Vertex will provide, or assess and approve, any electronic data capture (EDC) tools.

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. Data collected during the study will be recorded in a data capture system for each enrolled subject. Each subject's set of captured data records, once complete, will be signed and dated by the investigator.

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 data captured for the study/SAE Forms for completeness and clarity, 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 data captured for the study/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

Sites will use an EDC tool to record data for each enrolled subject.

It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported. 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, including the dates and details of study procedures, AEs, other observations, and subject status.

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 data reported to Vertex, including any changes made, to endorse the final submitted data for the subjects for whom the investigator is responsible.

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 clinical study report, written in accordance with the ICH E3 Guideline, will be submitted in accordance with local regulations.

14 REFERENCE

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX19-445-115	Version #: 2.2 AU and BE	Version Date: 21 December 2021
Study Title: A Phase 3b Open-label Study Evaluating the Safety of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Cystic Fibrosis Subjects		

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

Printed Name	Title
Signature	Date

15.2 Investigator Signature Page

Protocol #: VX19-445-115	Version #: 2.2 AU and BE	Version Date: 21 December 2021
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I have read Protocol VX19-445-115, Version 2.2 AU and BE, and agree to conduct the study according to its terms. I understand that all information concerning ELX, TEZ, IVA, and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date

1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol Addendum for Cystic Fibrosis

Cystic Fibrosis Studies for the Following Programs

[redacted]

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

[redacted]

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

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

Summary of Changes to Cystic Fibrosis Clinical Study Protocols

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

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

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

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

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

Protocol Change	Rationale for Change	Study Number
Addendum Version 3.0, dated 29 July 2020		
Assessments Unscheduled visit(s) will be permissible at the discretion of the investigator(s) or Vertex. The unscheduled visit(s) may be conducted at any time during the study (including after the protocol defined last study visit) in the event assessments specified to be collected at a scheduled visit were not collected due to COVID-19.	To ensure subject safety and/or to facilitate evaluation of safety and/or efficacy if assessments are not performed per the schedule in the protocol due to COVID-19.	[redacted] [redacted] [redacted] [redacted] VX19-445-115 [redacted] [redacted]
Implementaion of measures described in addenda versions 1.0 and 2.0, as applicable.	To ensure subject safety and/or to facilitate evaluation of safety and/or efficacy while maintaining study integrity and the safety of subjects and site personnel.	[redacted]

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

Protocol Change	Rationale for Change	Study Number
Addendum Version 2.0, dated 15 May 2020		
Assessments Weight and height/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] VX19-445-115 [redacted] [redacted] [redacted]

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

Protocol Change	Protocol Change	Protocol Change
Addendum Version 1.0, dated 24 April 2020		
Consenting of Subjects ICFs may be provided electronically or by post mail to subjects (and/or caregivers, as indicated per protocol). The subjects and/or caregivers will review the ICF with an appropriately qualified member of the investigator's team via telephone contact or video call. After this review, subjects and/or caregivers will consent (or assent, if applicable), and/or reconsent verbally and by signing and dating the ICF and returning it to the site via post mail. The signed and dated ICF will then be signed and dated by the investigator. Subjects participating in select studies may have the opportunity to enroll in longterm extension studies. Informed consent (or assent, if applicable), and/or reconsent for subjects (and/or caregivers, as indicated per protocol) may be obtained per the same process described above, as applicable.	To provide alternative methods of obtaining reconsent or consent, as applicable, while ensuring subject safety.	VX15-770-124 [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] VX19-445-115 [redacted]
In-home Visits and/or Telephone Contact Study visits may be conducted as in-home visits by qualified personnel as requested by participating sites on a per-subject basis. In addition, all subjects may be contacted by site personnel by telephone or video call, irrespective of in-home visits.	To provide subjects the opportunity to continue participation in the clinical studies while ensuring their safety by minimizing the risk to COVID-19 exposure through travel.	[redacted]

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

Protocol Change	Protocol Change	Protocol Change
Addendum Version 1.0, dated 24 April 2020		
Safety Assessments and Reporting Safety assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits (e.g., personnel from site or qualified health care agency). These assessments may include the following, as indicated per protocol, and per local regulation: • vital signs • pulse oximetry • [redacted] • 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 [redacted] • study drug administration [redacted] Investigators will review results (in-home and telephone) and contact subjects for follow-up as needed. All data will continue to be retained in the subject's source files. Any clinically significant finding (e.g., AE, SAE, laboratory abnormalities) will continue to be reported as indicated per protocol.	To assess the safety and tolerability of the CFTR modulator evaluated in the specific clinical study while ensuring subject safety. These safety assessments will continue to provide safety data while minimizing burden to subjects and site personnel. To clarify that despite these alternative measures, all adverse events and serious adverse events should be reported as indicated per protocol.	[redacted] VX19-445-115 [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		
[redacted] Other Assessments • ECGs [redacted], 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.	[redacted] VX19-445-115 [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] VX19-445-115 [redacted] [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; [redacted]