1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3b Open-label Study to Assess the Effect of Elexacaftor/Tezacaftor/Ivacaftor on Glucose Tolerance in Cystic Fibrosis Subjects with Abnormal Glucose Metabolism

Vertex Study Number: VX19-445-117

IND Number: 132547

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Date of Protocol: 26 April 2021 (Version 3.0)

Replaces Version 2.0, dated 22 September 2020

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

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Summary of Changes to the Protocol

The previous version of this protocol (Version 2.0, 22 September 2020) was amended to create the current version (Version 3.0, 26 April 2021). The protocol history is provided below.

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.1, 24 August 2020	Original version
Version 2.0, 22 September 2020	Removed option for use of remote measures at certain study visits such that those visits are to be performed in the clinic; clarified different glomerular filtration rates for subjects ≥18 years of age and subjects <18 years of age; clarified that during in-clinic visits, spirometry assessments may be performed on more than 1 spirometer, as applicable; removed sweat chloride assessment at Week 4; added language to allow use of remote measures in extenuating circumstances.
Version 3.0, 26 April 2021	Current version

Key changes in the current version of the protocol compared to Version 2.0 are summarized below.

Change and Rationale	**Affected Sections**
Updated the following Other Endpoints to clarify oral glucose tolerance test (OGTT) values (in mmol/L) and glucose ranges: • Change from baseline in percent of time spent in target blood glucose range of ≥70 to <140 mg/dL (≥3.89 to <7.77 mmol/L) as measured by 7-day continuous glucose monitoring (CGM) in subjects with cystic fibrosis-related diabetes (CFRD) at Week 48 • Change from baseline in selected CGM parameters (including but not limited to percent of time spent between ≥140 and <200 mg/dL [≥7.77 and <11.10 mmol/L], percent of time spent ≥200 mg/dL [≥11.10 mmol/L], and maximum amplitude of glucose excursions [MAGE]) in subjects with CFRD at Week 48	Synopsis, and Sections 7.3 and 12.3.3.5
Updated the definition of impaired glucose tolerance (IGT) to 2-hour post-OGTT blood glucose level ≥140 to <200 mg/dL (≥7.77 to <11.10 mmol/L) to eliminate a gap in glucose values in previous protocol versions, and to clarify both the glucose values (in mmol/L) and the dysglycemia categories.	Section 8.1
Updated the definition of CFRD to either fasting hyperglycemia (blood glucose level ≥126 mg/dL [≥7.00 mmol/L] after an 8-hour fast) or 2-hour post-OGTT blood glucose level ≥200 mg/dL (≥11.10 mmol/L) to eliminate a gap in glucose values in previous protocol versions, and to clarify both the glucose values (in mmol/L) and the dysglycemia categories.	Section 8.1
Updated text to state that height will be measured for all subjects at screening to correct an error in previous protocol versions.	Table 3-1 and Section 11.3.3
Added collection windows around the OGTT assessments and clarified that post-0 minute collection time points are defined as time after the start of ingestion of glucose solution to provide additional guidance on the execution of the OGTT assessment.	Table 3-1 and Table 3-2, and Section 11.3.1

Change and Rationale	Affected Sections
Removed specification that only subjects with CFRD will collect an insulin diary, such that any subject who uses insulin will collect an insulin diary, to allow for the possibility of both IGT and CFRD subjects to be on insulin.	Synopsis, Table 3-2, and Sections 7.3, 11.3.4, and 12.3.3.5
Added a waiver of the Safety Follow-up Visit for subjects who complete the Week 48 Visit and transition to a commercially available CFTR modulator regimen with 28 days after the last dose of study drug, given the possibility of commercial availability of ELX/TEZ/IVA in certain countries.	Section 9.1.3
Updated text that remote measures may be used for study visits at Week 4 and Week 12, but all other visits must be performed in the clinic, to provide clarity on the use of remote measures.	Section 9.1.7
Removed glyburide, nateglinide, and repaglinide from list of OATP1B1 and OATP1B3 substrates that should be used with caution to provide clarity and consistency within the protocol.	Section 9.5
Removed glimepiride and glipizide from list of CYP2C9 substrates that should be used with caution to provide clarity and consistency within the protocol.	Section 9.5
Added instruction for investigators to counsel subjects on safe withholding of insulins prior to each OGTT based on feedback from study sites.	Section 11.3.1
Added instruction for sites to record insulin use in the 24 hours prior to each OGTT, as insulin use may confound OGTT results.	Section 11.3.1

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

2 PROTOCOL SYNOPSIS

Title A Phase 3b Open-label Study to Assess the Effect of Elexacaftor/Tezacaftor/Ivacaftor on Glucose Tolerance in Cystic Fibrosis Subjects with Abnormal Glucose Metabolism

Brief Title A Study to Assess the Effect of ELX/TEZ/IVA on Glucose Tolerance in Subjects With Cystic Fibrosis (CF)

Clinical Phase and Clinical Study Type Phase 3b, investigation of glucose tolerance

Objective

Primary Objective

To evaluate the effect of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) on glucose tolerance in CF subjects with impaired glucose tolerance (IGT) or CF-related diabetes (CFRD)

Secondary Objective

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

Endpoints

Primary Endpoint

Change from baseline in 2-hour blood glucose levels following an oral glucose tolerance test (OGTT) to the average of Week 36 and Week 48

Secondary Endpoints

- Proportion of subjects with improvement in dysglycemia categorization (CFRD, IGT, normal glucose tolerance [NGT]) at Week 48
- Safety and tolerability of ELX/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry

Other Endpoints

- Change from baseline in sweat chloride (SwCl) through Week 48
- Absolute change in body mass index (BMI) from baseline at Week 48
- Absolute change in body weight from baseline at Week 48
- Change from baseline in hemoglobin A1c (HbA1c) and fructosamine at Week 48
- Change from baseline in insulin use (dose) at Week 48 in subjects using insulin
- Change from baseline in post-OGTT diabetes-related biomarkers (including insulin, C-peptide, glucagon, calculated indices of insulin secretion [insulinogenic index], and insulin resistance [HOMA-IR]) at Week 48
- Change from baseline in biomarkers of inflammation (including C-reactive protein [CRP]) at Week 48
- Change from baseline in biomarkers of pancreatic function (including fecal elastase-1 [FE-1] and serum immunoreactive trypsinogen [IRT]) at Week 48
- Change from baseline in post-OGTT incretin levels (including glucagon-like peptide 1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]) at Week 48
- Change from baseline in percent of time spent in target blood glucose range of ≥70 to <140 mg/dL (≥3.89 to <7.77 mmol/L) as measured by 7-day continuous glucose monitoring (CGM) in subjects with CFRD at Week 48

- Change from baseline in selected CGM parameters (including but not limited to percent of time spent between ≥140 and <200 mg/dL [≥7.77 and <11.10 mmol/L], percent of time spent ≥200 mg/dL [≥11.10 mmol/L], and maximum amplitude of glucose excursions [MAGE]) in subjects with CFRD at Week 48.

Number of Subjects

Approximately 60 subjects will be enrolled, of whom approximately 30 subjects will have IGT and 30 subjects will have CFRD.

Study Population

Male and female subjects with CF who are 12 years of age or older, heterozygous for the *F508del* mutation and an MF mutation (F/MF genotypes), with abnormal glucose tolerance as determined by OGTT at screening (classified as either IGT or CFRD). Among all subjects, approximately 50% may be enrolled while using insulin (≤0.3 units/kg/day).

Investigational Drug

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

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

Strength and route of administration: ELX 100-mg/TEZ 50-mg/IVA 75-mg fixed-dose combination (FDC) tablets, oral

Active substance: IVA (VX-770)

Activity: CFTR potentiator

Strength and route of administration: 150-mg tablets, oral

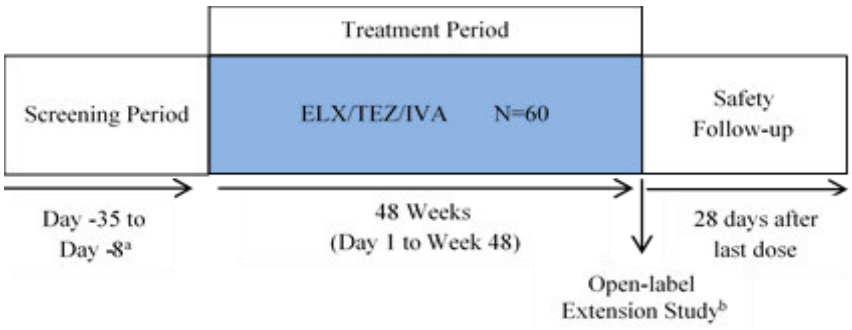
Study Duration

Excluding the Screening Period, the total study duration is approximately 52 weeks (48 weeks for the Treatment Period, and 4 weeks for the Safety Follow-up Period).

Study Design

This is a Phase 3b, open-label study in CF subjects 12 years of age and older with F/MF genotypes and abnormal glucose tolerance. A schematic of the study design is shown in Figure 2-1.

Figure 2-1 VX19-445-117 Study Design



ELX: elexacaftor; CFRD: CF-related diabetes; CGM: continuous glucose monitoring; IVA: ivacaftor; N: total sample size; TEZ: tezacaftor

[a] On Day -7, a CGM sensor will be inserted subcutaneously to assess baseline blood glucose levels for 7 days prior to the first dose of study drug in subjects with CFRD.

[b] Subjects who complete the visits in the Treatment Period, regardless of whether they are on a treatment interruption, will be offered the opportunity to enroll in an open-label extension safety study evaluating ELX/TEZ/IVA. The Safety Follow-up Visit is not required for subjects who complete the Week 48 Visit and have enrolled in an open-label study within 28 days after the last dose of study drug.

Subjects will receive ELX 200 mg once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h).

Assessments

Efficacy and PD:

- 2-hour OGTT
- SwCl
- BMI
- Weight
- Height
- Diabetes-related blood biomarkers collection
- Insulin use diary for subjects using insulin
- CGM (subjects with CFRD only)

Safety: AEs, clinical laboratory assessments, 12-lead ECGs, vital signs, pulse oximetry, ophthalmologic examinations (for subjects <18 years of age on the date of informed consent), and physical examinations (PEs)

Other:

- Spirometry
- Fecal sample collection
- Other blood biomarkers collection

Statistical Analyses

Statistical analysis details will be provided in the Statistical Analysis Plan (SAP), which will be finalized before the clinical database lock.

The primary null hypothesis to be tested is that the mean change from baseline in 2-hour blood glucose levels following OGTT to the average of Week 36 and Week 48 is equal to zero. Assuming a within group SD of 45 mg/dL and a 10% dropout rate at Week 48, a sample size of 60 subjects will have more than 95% power to detect a mean decrease from baseline of -30 mg/dL in 2-hour blood glucose levels

post-OGTT to the average of Week 36 and Week 48, based on a 2-sided, 1-sample *t*-test at a significance level of 0.05 using the EAST software Version 6.4.

The primary analysis will be based on a mixed-effects model for repeated measures (MMRM) with change from baseline in 2-hour post-OGTT blood glucose levels at Weeks 24, 36, and 48 as the dependent variable. The model will include visit as a fixed effect, and will be adjusted for main covariates as appropriate. The primary result obtained from the model will be the estimated mean change from baseline to the average of Week 36 and Week 48. The estimated change at each visit and the mean change to the average of Week 36 and Week 48 along with the 2-sided 95% CI and *P* value will be provided.

3 SCHEDULE OF ASSESSMENTS

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

Table 3-1 Study VX19-445-117: Screening

Event/Assessment	Screening Visit Day -35 to Day -8	Comments
Study visit	X	The Screening Visit must be performed in the clinic.
Informed consent (and assent, if applicable)	X	Electronic or remote consent may be used, if permitted by local regulations.
Demographics	X	Section 11.1
Medical history	X	Section 11.1
Medications review	X	Information regarding medications taken within 56 days before the Screening Visit will be collected (Section 9.5).
Height and weight	X	Measured with shoes off (Section 11.3.3).
Vital signs and pulse oximetry	X	Collected after the subject has been at rest for at least 5 minutes (Section 11.4.3).
Ophthalmologic examination	X	Conducted by an ophthalmologist or optometrist for subjects <18 years of age on the date of informed consent (Section 11.4.5).
Complete physical examination	X	Section 11.4.3
12-lead ECG	X	Performed prior to any procedure that may affect heart rate (e.g., blood draws) and after subject has been at rest for at least 5 minutes (Section 11.4.4).
Sweat chloride	X	Section 11.3.5
Spirometry	X	Performed pre- or post-bronchodilator (Section 11.2.1)
CF genotype	X	If the *CFTR* genotype result is not received before the first dose of study drug, a previous *CFTR* genotype laboratory report may be used to establish eligibility (Section 8.1). Subjects who have been enrolled whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).
Serum pregnancy (all female subjects)	X	Section 11.4.2
Serum chemistry (including cholesterol and thyroid-stimulating hormone)	X	
Hematology	X	
Coagulation	X	
Urinalysis	X	
Oral glucose tolerance test (OGTT)	X	If permitted by local regulations, subjects may provide informed consent remotely to begin fasting (except water and allowed medications other than prednisone and prednisolone) at least 8 hours before the OGTT at the Screening Visit. Blood glucose levels will be measured at 0, 30 (±5), 60 (±5), 90 (±5), and 120 (±5) minutes after the start of consuming 1.75 g/kg of body weight (maximum of 75 g total) of glucose solution (Section 11.3.1).
OGTT blood biomarkers collection	X	Collected on the same day as the OGTT (Section 11.3.1).
Fecal sample collection	X	Fecal sample may be collected at the site during the Screening Visit, or at any time point prior to the first dose of study drug (Section 11.2.2).

Table 3-1 Study VX19-445-117: Screening

Event/Assessment	Screening Visit Day -35 to Day -8	Comments
Adverse events	**Continuous, From the Date of Informed Consent through Completion of Study Participation**	Section 13.1; completion of study participation is defined in Section 9.1.6.

CF: cystic fibrosis; OGTT: oral glucose tolerance test

Table 3-2 Study VX19-445-117: Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day -7 (± 1 day)[b]	Treatment Period: Day 1	Week 4 (± 5 days)	Weeks 8, 16, 20, 28, 32, 40, 44 (± 5 days)	Week 12 (± 5 days)	Week 24 (± 5 days)	Week 36 (± 5 days)	Week 48 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)[c]	Comments
Study visit	X	X	X		X	X	X	X	X	X	The Week 4 and Week 12 visits may be performed either in the clinic or as a home health visit, if permitted by local regulations. See Section 9.1.7 for use of remote measures in extenuating circumstances. All home health visits must have a consultation between the subject and investigator (i.e., in person, phone, or telemedicine video conference) within 1 business day after the home health visit; this consultation can be outside the visit window.
Telephone contact or telemedicine video conference				X							Assess subject's status, any AEs, concomitant medications, treatments, and procedures.

[a] All assessments will be performed before dosing unless noted otherwise.
[b] The Day -7 Visit only applies to subjects with CFRD.
[c] The Safety Follow-up Visit is not required for subjects who complete the Week 48 Visit and have enrolled in an open-label study within 28 days.

Table 3-2 Study VX19-445-117: Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day -7 (± 1 day)[b]	Treatment Period: Day 1	Week 4 (± 5 days)	Weeks 8, 16, 20, 28, 32, 40, 44 (± 5 days)	Week 12 (± 5 days)	Week 24 (± 5 days)	Week 36 (± 5 days)	Week 48 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)[c]	Comments
Safety and Efficacy Assessments											
Ophthalmologic examination								X at or up to 4 weeks before	X		Conducted by an ophthalmologist or optometrist for subjects <18 years of age on the date of informed consent (Section 11.4.5). Subjects who complete at least 12 weeks of study drug treatment will have a single ophthalmologic examination at either the ETT or Week 48 Visit, whichever comes first.
Complete physical examination		X						X	X		Symptom-directed physical examinations will occur at any time during the study if deemed necessary by the investigator (Section 11.4.3).
Height and weight		X	X		X	X	X	X	X	X	Measured with shoes off. Height will only be collected for subjects <21 years of age on the date of informed consent (Section 11.3.3).
Vital signs and pulse oximetry		X	X		X	X	X	X	X	X	Collected after the subject has been at rest for at least 5 minutes (Section 11.4.3).

Table 3-2 Study VX19-445-117: Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day -7 (± 1 day)[b]	Treatment Period							ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)[c]	Comments
		Day 1	Week 4 (± 5 days)	Weeks 8, 16, 20, 28, 32, 40, 44 (± 5 days)	Week 12 (± 5 days)	Week 24 (± 5 days)	Week 36 (± 5 days)	Week 48 (± 5 days)			
12-lead ECG		X				X		X	X	X	Performed prior to any procedure that may affect heart rate (e.g., blood draws) and after subject has been at rest for at least 5 minutes (Section 11.4.4).
Oral glucose tolerance test (OGTT)		X				X	X	X			After at least an 8-hour fast (except water and allowed medications other than prednisone and prednisolone). Blood glucose levels will be measured at 0, 30 (±5), 60 (±5), 90 (±5), and 120 (±5) minutes after the start of consuming 1.75 g/kg of body weight (maximum of 75 g total) of glucose solution (Section 11.3.1).
OGTT blood biomarkers collection		X				X	X	X			Collected on the same days as the OGTT (Section 11.3.1)
CGM sensor inserted *(subjects with CFRD only)*	X	X			X	X	X	X			The CGM sensor will be inserted and worn for approximately 7 days (Section 11.3.2).
Sweat chloride		X				X		X	X		Section 11.3.5
Blood collection for HbA1c and fructosamine		X	X		X	X	X	X	X		

Table 3-2 Study VX19-445-117: Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day -7 (± 1 day)[b]	Treatment Period							ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)[c]	Comments
		Day 1	Week 4 (± 5 days)	Weeks 8, 16, 20, 28, 32, 40, 44 (± 5 days)	Week 12 (± 5 days)	Week 24 (± 5 days)	Week 36 (± 5 days)	Week 48 (± 5 days)			
Pregnancy test (all female subjects)		Urine	Urine	Urine	Urine	Urine	Urine	Urine	Serum	Serum	At telephone contacts, a urine pregnancy test will be performed with a home kit provided by the study site. Results will be reported to the site by telephone (Section 11.4.2).
Serum chemistry		X	X		X	X	X	X	X	X	Section 11.4.2
Hematology		X	X		X	X	X	X	X	X	
Coagulation		X				X		X	X	X	
Urinalysis		X						X	X	X	
Insulin diary for insulin users		X	X		X	X	X	X	X		At each study visit the subject will provide the diary for documentation of insulin use (Section 11.3.4)
Adverse events	**Continuous, From the Date of Informed Consent through Completion of Study Participation**										Completion of study participation is defined in Section 9.1.6.
Medications review	**Continuous, From the Date of Informed Consent through Completion of Study Participation**										
Treatment and procedures review	**Continuous, From the Date of Informed Consent through Completion of Study Participation**										
Other Assessments											
Blood biomarker collection for pancreatic markers		X	X		X	X		X	X		Section 11.2.3

Table 3-2 Study VX19-445-117: Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day -7 (± 1 day)[b]	Treatment Period							ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)[c]	Comments
		Day 1	Week 4 (± 5 days)	Weeks 8, 16, 20, 28, 32, 40, 44 (± 5 days)	Week 12 (± 5 days)	Week 24 (± 5 days)	Week 36 (± 5 days)	Week 48 (± 5 days)			
Blood biomarker collection for inflammatory markers		X	X		X	X		X	X		Section 11.2.3
Fecal sample collection		X				X		X			Samples may be collected by the subject or the subject's caregiver up to 48 hours before the study visit at home and brought to the study visit (Section 11.2.2). The Day 1 sample must be collected predose; others may be collected pre- or postdose. Subjects who provide a fecal sample at the Screening Visit, or at any time point prior to the first dose of study drug, do not need to provide a sample on Day 1.

Table 3-2 Study VX19-445-117: Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day -7 (± 1 day)[b]	Treatment Period: Day 1	Week 4 (± 5 days)	Weeks 8, 16, 20, 28, 32, 40, 44 (± 5 days)	Week 12 (± 5 days)	Week 24 (± 5 days)	Week 36 (± 5 days)	Week 48 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)[c]	Comments
Spirometry		X	X			X		X	X		Performed pre-bronchodilator, before the AM dose, and at approximately the same time at each visit (Section 11.2.1). During in-clinic visits, spirometry assessments may be performed on more than one spirometer, as applicable.
Study Drug Administration											
Study drug dosing		ELX/TEZ/IVA Day 1 through evening before Week 48 Visit									Administered within approximately 30 minutes of consuming fat-containing food (e.g., standard "CF" meal or snack) (Section 9.6.1). On scheduled visits, the morning dose of study drug will be administered under the supervision of site medical staff or a home health nurse after predose assessments have been completed (food to be provided by site on in-clinic visit days).
Study drug count			X		X	X	X	X	X		

Table 3-2 Study VX19-445-117: Treatment Period and Safety Follow-up Visit

		Treatment Period									
Event/ Assessment[a]	Day -7 (± 1 day)[b]	Day 1	Week 4 (± 5 days)	Weeks 8, 16, 20, 28, 32, 40, 44 (± 5 days)	Week 12 (± 5 days)	Week 24 (± 5 days)	Week 36 (± 5 days)	Week 48 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)[c]	Comments

AE: adverse event; CF: cystic fibrosis; CFRD: cystic fibrosis related diabetes; CGM: continuous glucose monitoring; ELX: elexacaftor; ETT: early termination of treatment; HbA1c: hemoglobin A1c; IRT: immunoreactive trypsinogen; IVA: ivacaftor; OGTT: oral glucose tolerance test; TEZ: tezacaftor

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List of Abbreviations

Abbreviation	Definition
ADL	activities of daily living
AEs	adverse events
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	Aspartate transaminase
β	beta, apparent elimination rate constant
BMI	body mass index
CD	compact disc
CF	Cystic Fibrosis
CFRD	CF related diabetes
CFTR	CF transmembrane conductance regulator protein
CFTR	CF transmembrane conductance regulator gene
CGM	continuous glucose monitoring
CI	confidence interval
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
ELX	elexacaftor
ETT	Early Termination of Treatment
EU	European Union
F/MF	*F508del* mutation and a minimal function mutation
F508del	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FE-1	fecal elastase-1
$FEF_{25\%-75\%}$	forced expiratory flow, midexpiratory phase
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GIP	glucose-dependent insulinotropic polypeptide
GLI	Global Lung Function Initiative
GLP-1	glucagon-like peptide 1
GPP3	Good Publication Practices

Abbreviation	Definition
GPS	Global Patient Safety
HbA1c	hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IGT	impaired glucose tolerance
IMP	investigational medicinal product
IND	Investigational New Drug (application) (US)
IRB	institutional review board
IRT	immunoreactive trypsinogen
IVA	ivacaftor
IWRS	interactive web response system
LS	least squares
LUM	lumacaftor
MAGE	maximum amplitude of glucose excursions
max	maximum value
min	minimum value
MMRM	mixed-effects model for repeated measures
n	size of subsample
N	total sample size (e.g., number of subjects treated)
NGT	normal glucose tolerance
OATP1B1	organic anion transporting polypeptide 1B1
OATP1B3	organic anion transporting polypeptide 1B3
OGTT	oral glucose tolerance test
P	probability
PC	publication committee
PD	pharmacodynamic
PEs	physical examinations
P-gp	P-glycoprotein
PIs	principal investigators
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
q12h	every 12 hours
qd	once daily
QTcF	QT interval corrected by Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	steering committee
SD	standard deviation
SET	Study Execution Team
SUSARs	suspected, unexpected, serious adverse events
SwCl	sweat chloride

Abbreviation	Definition
TE	Treatment-emergent
TEAEs	treatment emergent adverse events
TEZ	tezacaftor
t-test	statistical test used when the independent variable is binary and the dependent variable is continuous
ULN	upper limit of normal
US	United States
USA	United States of America
WHO-DD	World Health Organization-Drug Dictionary

5 INTRODUCTION

5.1 Background

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

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

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

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

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

5.2 Study Rationale

Abnormal glucose metabolism is a common complication from CF, and CF-related diabetes (CFRD) reaches a prevalence of approximately 50% of adults overall and approximately 80% of adults with a severe genotype (i.e., heterozygous for *F508del* and a minimal function mutation [F/MF])[8]. The primary deficiency is one of impaired insulin secretion due to loss of pancreatic beta cell (insulin producing) mass and function. Multiple mechanisms contribute to pancreatic destruction, including impaired bicarbonate/fluid secretion and thickened mucus (mucoviscidosis), which blocks exocrine ducts and results in fatty/fibrotic replacement of the majority of the pancreas. Over time, inflammation is believed to further impair the function of reduced endocrine islet cell mass and function. Genetics and other as yet unknown mechanisms are also believed to play a role in the progression to CFRD, and the need for exogenous insulin treatment, which is currently the standard of care. Patients who develop impaired glucose tolerance (IGT) or CFRD are known to have faster decline in lung function, higher mortality, and overall significantly increased burden of disease[8]. The present study is designed to evaluate the

effect of ELX/TEZ/IVA on impaired glucose homeostasis in CF subjects with abnormal glucose metabolism.

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the effect of ELX/TEZ/IVA on glucose tolerance in CF subjects with IGT or CFRD

6.2 Secondary Objective

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

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Change from baseline in 2-hour blood glucose levels following an oral glucose tolerance test (OGTT) to the average of Week 36 and Week 48

7.2 Secondary Endpoints

- Proportion of subjects with improvement in dysglycemia categorization (CFRD, IGT, normal glucose tolerance [NGT]) at Week 48
- Safety and tolerability of ELX/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry

7.3 Other Endpoints

- Change from baseline in sweat chloride (SwCl) through Week 48
- Absolute change in body mass index (BMI) from baseline at Week 48
- Absolute change in body weight from baseline at Week 48
- Change from baseline in hemoglobin A1c (HbA1c) and fructosamine at Week 48
- Change from baseline in insulin use (dose) at Week 48 in subjects using insulin
- Change from baseline in post-OGTT diabetes-related biomarkers (including insulin, C-peptide, glucagon, calculated indices of insulin secretion [insulinogenic index], and insulin resistance [HOMA-IR]) at Week 48
- Change from baseline in biomarkers of inflammation (including C-reactive protein [CRP]) at Week 48
- Change from baseline in biomarkers of pancreatic function (including fecal elastase-1 [FE-1] and serum immunoreactive trypsinogen [IRT]) at Week 48
- Change from baseline in post-OGTT incretin levels (including glucagon-like peptide 1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]) at Week 48
- Change from baseline in percent of time spent in target blood glucose range of ≥70 to <140 mg/dL (≥3.89 to <7.77 mmol/L) as measured by 7-day continuous glucose monitoring (CGM) in subjects with CFRD at Week 48
- Change from baseline in selected CGM parameters (including but not limited to percent of time spent between ≥140 and <200 mg/dL [≥7.77 and <11.10 mmol/L], percent of time

spent ≥200 mg/dL [≥11.10 mmol/L], and maximum amplitude of glucose excursions [MAGE]) in subjects with CFRD at Week 48

8 STUDY POPULATION

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

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

8.1 Inclusion Criteria

1. Subject (or 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. Subjects (male and female) 12 years of age or older on the date of informed consent.
4. Subjects heterozygous for *F508del* and an MF mutation (F/MF genotypes, see Appendix A for definition and non-exhaustive list of eligible MF mutations).
   a. Genotype should be confirmed at the Screening Visit.
   b. If the screening *CFTR* genotype result is not received before the first dose of study drug, a previous *CFTR* genotype laboratory report may be used to establish eligibility.
   c. Subjects who have been enrolled and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).
5. Forced expiratory volume in 1 second (FEV_1) value ≥30% of predicted mean for age, sex, and height (equations of the Global Lung Function Initiative [GLI])[9] at the Screening Visit (spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria[10] for acceptability and repeatability) and stable CF disease as judged by the investigator.
6. Willing to remain on a stable CF treatment regimen (other than *CFTR* modulators) through completion of study participation.
7. Abnormal glucose tolerance as determined by an OGTT, classified as either IGT (defined as 2-hour post-OGTT blood glucose level ≥140 to <200 mg/dL [≥7.77 to <11.10 mmol/L]) or CFRD (defined as either fasting hyperglycemia [blood glucose level ≥126 mg/dL (≥7.00 mmol/L) after an 8-hour fast] or 2-hour post-OGTT blood glucose level ≥200 mg/dL [≥11.10 mmol/L]).

8.2 Exclusion Criteria

1. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This includes, but is not limited to, the following:
   - Clinically significant liver cirrhosis with or without portal hypertension
   - Solid organ or hematological transplantation

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

2. Type 1 or Type 2 diabetes.
3. Duration of CFRD ≥5 years.
4. Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject (as deemed by the investigator).
5. Any of the following abnormal laboratory values at screening:
   - Hemoglobin <10 g/dL
   - Total bilirubin ≥2 × upper limit of normal (ULN)
   - Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN
   - Abnormal renal function defined as glomerular filtration rate ≤50 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease Study Equation)[11, 12] for subjects ≥18 years of age and ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation)[13] for subjects <18 years of age
6. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug).
7. Lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For subjects who have had a history of a positive culture, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
   - The subject has not had a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent.
   - The subject has had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent.
8. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug (Day 1).
9. Ongoing or prior participation in an investigational drug study (including studies investigating ELX with or without coadministration of other study drugs) within 28 days of the Screening Visit.
   - A washout period of 5 terminal half-lives of the previous investigational study drug, or 28 days, whichever is longer, must elapse before the Screening Visit.

- The duration of the elapsed time may be longer if required by local regulations.

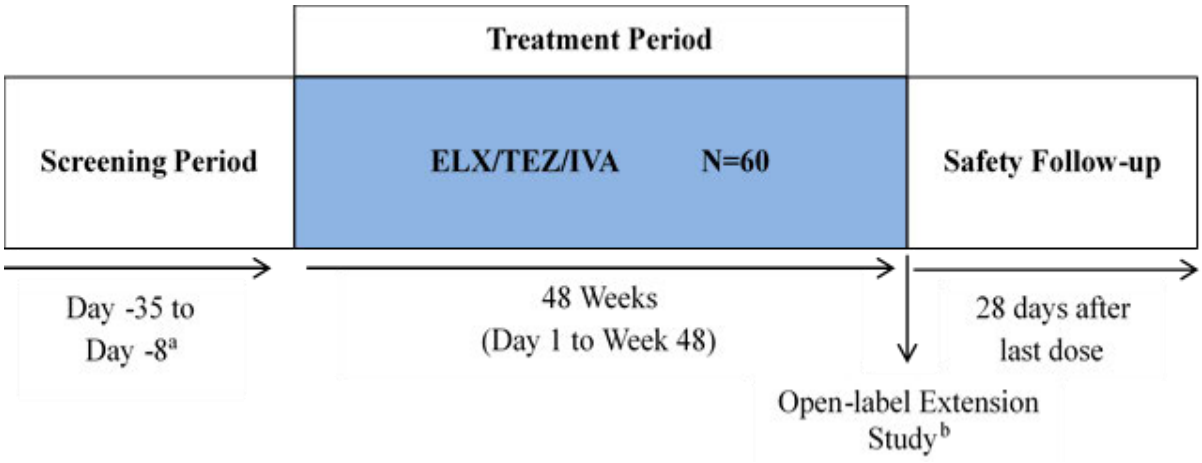
10. Use of restricted medication (including antidiabetic medication other than insulin, which must be at a dose no greater than 0.3 units/kg/day) within specified duration before the first dose of study drug as defined in Table 9-1.
11. BMI ≥30 kg/m^2 at the Screening Visit.
12. Pregnant and breast-feeding females. All female subjects regardless of childbearing potential status (Section 11.4.6) must have a negative pregnancy test at the Screening Visit and the Day 1 Visit.
13. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site. However, an adult (aged 18 years or older) who is a relative of a study staff member may be enrolled in the study provided that:
    - the adult lives independently of and does not reside with the study staff member, and
    - the adult participates in the study at a site other than the site at which the family member is employed.

9 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 3b, open-label study in CF subjects 12 years of age and older with F/MF genotypes and abnormal glucose tolerance (Figure 9-1). Approximately 60 subjects (F/MF genotypes) will be enrolled, of whom approximately 30 subjects will have IGT and 30 subjects will have CFRD. During the Treatment Period, subjects will be administered ELX/TEZ/IVA for approximately 48 weeks. All subjects will receive ELX 200 mg once daily (qd)/TEZ 100 mg qd/ IVA 150 mg every 12 hours (q12h).

Figure 9-1 VX19-445-117 Study Design



ELX: elexacaftor; CFRD: CF-related diabetes; CGM: continuous glucose monitoring; IVA: ivacaftor; N: total sample size; TEZ: tezacaftor

[a] On Day -7, a CGM sensor will be inserted subcutaneously to assess baseline blood glucose levels for 7 days prior to the first dose of study drug in subjects with CFRD.

[b] Subjects who complete the visits in the Treatment Period, regardless of whether they are on a treatment interruption, will be offered the opportunity to enroll in an open-label extension safety study evaluating ELX/TEZ/IVA. The Safety Follow-up Visit is not required for subjects who complete the Week 48 Visit and have enrolled in an open-label study within 28 days after the last dose of study drug.

9.1.1 Screening

Screening Visit assessments are listed in Table 3-1.

Screening will occur within 35 days before administration of study drug. The investigator (or an appropriate authorized designee) will obtain informed consent from each subject.

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

9.1.1.1 Repetition of Screening Assessment(s)

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

9.1.1.2 Rescreening

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

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

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

9.1.1.3 Extension of Screening Period Window

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

- Repetition of the Screening Period assessments (Section 9.1.1.1)
- Unexpected operational or logistic delays, or to meet the eligibility criteria
- Scheduling of ophthalmologic examination (Section 11.4.5)

9.1.2 Treatment Period

Treatment Period assessments are listed in Table 3-2.

The Treatment Period will last approximately 48 weeks. Study drug administration details are provided in Section 9.6.

9.1.3 Follow-up

The Safety Follow-up Visit is scheduled to occur 28 (± 7) days after the last dose of study drug. The Safety Follow-up Visit is not required for subjects who complete the Week 48 Visit and enroll in the open-label extension safety study, or who transition to a commercially available CFTR modulator regimen, within 28 days after the last dose of study drug.

9.1.4 Early Termination of Treatment

If a subject prematurely discontinues study treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit.

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.

9.1.5 Lost to Follow-up

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

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

9.1.6 Completion of Study Participation

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

- For subjects who complete the Treatment Period and enter an open-label extension safety study within 28 days of the Week 48 Visit: the Week 48 Visit
- For subjects who complete the Treatment Period and do not enter an open-label extension safety study within 28 days of the Week 48 Visit: the Safety Follow-up Visit
- For subjects who prematurely discontinue study drug treatment but do not withdraw consent (and assent, as applicable): the latest of the ETT Visit or Safety Follow-up Visit (if required)
- For subjects who withdraw consent or assent: date of withdrawal of consent or assent, whichever is earlier (Section 9.9)

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

The end of study is defined in Section 13.2.9.

9.1.7 Use of Remote Measures

Remote measures may be used for study visits at Week 4 and Week 12 (see Table 3-2). All other visits must be performed in the clinic.

Whenever local regulations or site practice do not allow remote measures, visits will be conducted at the site. However, under extenuating circumstances, remote measures may be implemented (e.g., if a subject is unable to travel to the study site due to safety concerns and/or local restrictions related to COVID-19 or other emerging events). The decision whether to conduct a study visit remotely or in clinic will be at the discretion of the investigator; if the investigator determines that study visits will be conducted remotely, the medical monitor should be notified. Under extenuating circumstances, the Screening visit (including initial consent) and Day 1 visits must still be performed in the clinic.

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

- Consent and reconsent may be obtained electronically (or verbally, with follow-up electronic/written confirmation), as allowed by local regulations.
- Study drug may be shipped directly from the site to the subject, as applicable and as allowed by local regulations.
- Under extenuating circumstances, study visits (except Screening and Day 1) may be conducted as in-home visits by qualified personnel. All visits must have a consultation between the subject and investigator (i.e., in person, phone, or telemedicine video conference) within 1 business day after the home health visit, which can be outside the visit window.
- Study assessments may be performed or overseen by qualified personnel conducting the in-home visits.
- Remote monitoring visits may be implemented as applicable (including remote source data verification) and as allowed per local regulations.

9.2 Method of Assigning Subjects to Treatment Groups

This is an open-label study.

9.3 Rationale for Study Elements

9.3.1 Study Design

In patients with CF, IGT (a form of prediabetes) and then CFRD develops progressively, starting as early as age 10, and without known remission.[14] Once the diagnosis of IGT is made, patients have an approximately 4 to 11 × increased risk of developing CFRD over a 3 to 4 year observation period[15, 16], at which point insulin treatment is often started. Thus, the diagnoses of IGT and CFRD are considered robust and clinically relevant categories of disease.[16] An open-label study design is therefore appropriate to ascertain the effects of ELX/TEZ/IVA through within-group comparisons over 48 weeks. A 48-week treatment period is expected to be sufficient to determine the maximum treatment effect of ELX/TEZ/IVA on changes in glucose tolerance (OGTT) in CF subjects with IGT or CFRD, and follows a similar open-label study design in which Orkambi was found to improve glucose tolerance in subjects with IGT and CFRD.[17] Due to the known variability in the OGTT in patients with IGT and CFRD, 2 OGTTs at baseline (Screening and Day 1), 1 OGTT at Week 24, and 2 OGTTs at the end of the study (Weeks 36 and 48) will be performed.[18]

9.3.2 Study Population

This study will enroll CF subjects with F/MF genotypes, 12 years of age and older. A pivotal Phase 3 study demonstrated efficacy and safety of ELX/TEZ/IVA in CF subjects with F/MF genotypes 12 years of age and older. The F/MF population has the highest incidence of abnormal glucose tolerance, as defined by an OGTT, including IGT and CFRD. This is due to stereotypical progression of pancreatic disease, including blocked acinar ducts, atrophy of the exocrine pancreas, loss of endocrine islets, inflammation, additional genetic factors, and other potential mechanisms as described above. Patients with F/MF genotypes therefore offer a population of patients who are naive to CFTR modulator treatment and have prevalent endocrine disease (IGT/CFRD) that is amenable to investigation.

This study will utilize both the OGTT and CGM to evaluate the effect of ELX/TEZ/IVA on abnormal glucose homeostasis in subjects with CF and F/MF genotypes.

9.3.3 Study Drug Dose

The dose of ELX/TEZ/IVA evaluated in the pivotal Phase 3 study in subjects with F/MF genotypes ≥12 years of age (ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h) was generally safe and well tolerated and resulted in clinically meaningful improvements compared to placebo in endpoints including ppFEV$_1$ (LS mean treatment difference of 14.3 percentage points [p<0.0001] for absolute change from baseline) and SwCl (LS mean treatment difference of -41.8 mmol/L [p<0.0001] for absolute change from baseline) through 24 weeks. This dose of ELX/TEZ/IVA is approved in some regions for the treatment of CF and will be used for all subjects enrolled in this study.

9.3.4 Rationale for Study Assessments

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

An OGTT will be performed to assess changes in glucose levels post-oral glucose challenge, including the 2-hour time point. The OGTT is a standard procedure recommended annually for CF patients by age 10, and any other time CFRD is suspected. CGM will be performed in subjects with CFRD only to assess dynamic, free-ranging changes in capillary glucose levels and for associations with changes in other biomarkers or parameters. Serum biomarkers of glucose homeostasis (insulin, glucagon, incretins) are standard biomarkers for mechanistic studies involving patients with diabetes. Changes in $ppFEV_1$ have been correlated with glucose control parameters (i.e., CGM)[15], and will be useful to establish extrapulmonary (independent of lung) efficacy, and also confirm a positive drug effect throughout the study. SwCl is a standard pharmacodynamic (PD) assessment for studies involving subjects with CF, and this PD marker in skin can be correlated with pulmonary and extrapulmonary (diabetes-related) endpoints in order to advance the understanding of systemic efficacy of ELX/TEZ/IVA.

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.

Table 9-1 Prohibited Medications

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

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

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

9.5 Prior and Concomitant Medications

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

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

- Subjects should remain on a stable treatment regimen for their CF from 28 days before the Day 1 Visit through completion of study participation. Stable treatment regimen is defined as the current treatment regimen for CF that subjects have been following for at least 28 days before the Day 1 Visit. Subjects should not initiate long-term treatment with new medication from 28 days before the Day 1 Visit through completion of study participation. Guidelines for stable treatment regimens for CF are as follows:
    - Subjects who are taking inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
    - Subjects who cycle onto and off of an inhaled antibiotic should continue on their prior schedule. The timing of the first dose of study drug on the Day 1 Visit should be synchronized as closely as possible (e.g., not more than ± 3 days) to the first day in the cycle onto the inhaled antibiotic.
    - Subjects who alternate between 2 different inhaled antibiotics should remain on the same cycling schedule during the study. The timing of the first dose of study drug on the Day 1 Visit should be synchronized as closely as possible (e.g., not more than ± 3 days) to the first day in the cycle onto 1 of the inhaled antibiotics.
- Subjects may receive doses of prednisone or prednisolone of up to 10 mg/day chronically, or up to 60 mg daily for up to 5 days; however, these doses may not be administered during a pre-OGTT fasting period.
- ELX may inhibit OATP1B1 and OATP1B3, which may increase the exposure of medicinal products that are substrates for these transporters. Substrates such as statins 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 should be used with caution.
- Information about bronchodilator use during the study will be collected and documented. Subjects who are using a bronchodilator should have their spirometry assessments performed according to the guidelines provided in Section 11.2.1.

9.6 Administration

9.6.1 Dosing

Study drug tablets will be administered orally as ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h.

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

1. It is recommended that the dose be taken within approximately 30 minutes of the start of the meal or snack.
2. All doses of study drug (morning and evening, as applicable) should be administered at approximately every 12 hours (± 2 hours) on each dosing occasion (e.g., if the morning doses of study drug are administered at 08:00 hour on Day 1, all subsequent morning doses should be administered between 06:00 hour and 10:00 hour).
3. At the Day 1 Visit, all subjects will be observed for 2 hours after the morning dose of the study drug.
4. On days of scheduled visits, the morning dose of study drug will be administered under the supervision of site medical staff or a home health nurse after predose assessments have been completed. The meal or snack will be provided by the site on in-clinic visit days for the morning dose of study drug.
5. For visits after the Day 1 Visit, subjects will be instructed to return all used and unused study drug to the site or the home health nurse; study drug will be dispensed at each visit, as appropriate.
6. At the Week 48 Visit, the morning dose of study drug will NOT be administered. The last dose of study drug will be the evening dose administered the day before the Week 48 Visit.

9.6.2 Missed Doses

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

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

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

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

9.7 Dose Modification for Toxicity

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

9.8 Study Drug Interruption and Stopping Rules

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

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

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

9.8.1 Liver Function Tests

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

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

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

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

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

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

Study drug administration **must be discontinued** if the following 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 (Section 13.1.1.4), or is an SAE. Investigators should consider additional evaluation including laboratory testing (e.g., complete blood count with differential, liver function tests), photographs of the rash, and dermatology consultation. The investigator may consider resumption of study drug if considered clinically appropriate.

9.9 Removal of Subjects

Subjects (or subjects' parent/legal guardian) may withdraw from the study at any time at their own request. Subjects may be withdrawn 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 (or is withdrawn by parent/legal guardian) from study drug treatment will continue to be followed unless the subject (or parent/legal guardian) withdraws consent.

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

- Has a screening *CFTR* genotype that does not confirm study eligibility if a previous *CFTR* genotype laboratory report was used to establish eligibility. These subjects must be discontinued from the study (Section 8.1)
- Meets any of the stopping (discontinuation) criteria (Section 9.8)
- Becomes pregnant (Section 11.4.6.2)

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

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

9.10 Replacement of Subjects

Subjects who withdraw or are withdrawn during the study drug treatment period 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. An interactive web response system (IWRS) will be used to dispense study drug.

10.2 Packaging and Labeling

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

10.3 Study Drug Supply, Storage, and Handling

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

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

Table 10-1 Study Drug

Drug Name, Dosing Form, Route	Tablet 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
Note: See Section 9.6 for details on study drug administration.

10.4 Drug Accountability

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

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

10.5 Disposal, Return, or Retention of Unused Drug

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

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

10.6 Compliance

To ensure treatment compliance, the investigator or designee will supervise all study drug dosing that occurs at the site or in the subject's home at required visits. At each visit, site medical staff/home health nurses will review that the subject is compliant with study drug dosing and remind the subject and their parent or legal guardian of study drug dosing requirements. Compliance will also be assessed by ongoing study drug count.

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

10.7 Blinding and Unblinding

This is an open-label study; however, subjects and their parent/legal guardian should not be informed of their study-related CGM, SwCl, spirometry, FE-1, and blood biomarker results during the Treatment Period, regardless if the subject permanently discontinues.

11 ASSESSMENTS

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

11.1 Subject and Disease Characteristics

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

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

11.2 Other Assessments

These data will be used for internal exploratory purposes and may or may not be included in the clinical study report (CSR).

11.2.1 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines/European Respiratory Society Guidelines[10] and according to the additional guidelines that follow.

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

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

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

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

Spirometers will be provided to be used for all study assessments. At scheduled visits, spirometry assessments may be performed on more than one spirometer, as applicable. Spirometry data will be transmitted to a centralized spirometry service for quality review. The investigator's assessment of the spirometry results will be used for the screening assessment and determination of eligibility.

See Section 10.7 for information about access to spirometry results.

The measured spirometric values listed below will be converted to percent predicted values using the standard equations of GLI.[9]

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

11.2.2 Fecal Sample Collection

FE-1 will be measured to assess exocrine pancreatic function.

Fecal samples may be collected by site medical staff or a home health nurse during the study visit; alternatively, at all visits except the Screening Visit, samples may be collected by the

subject or the subject's caregiver up to 48 hours before the study visit at home and brought to the study visit. The Day 1 sample must be collected predose; others may be collected pre- or postdose. Subjects who provide a fecal sample at the Screening Visit, or at any time point prior to the first dose of study drug, do not need to provide a sample on Day 1.

See Section 10.7 for information about access to FE-1 results.

Instructions for the collection, processing, storage, and shipment of fecal samples will be provided in a separate Laboratory Manual.

11.2.3 Other Blood Biomarker Collection

Pancreatic markers, including but not limited to IRT, will be measured in blood to assess exocrine pancreatic function. Inflammatory markers, including but not limited to CRP, will be measured in blood to assess inflammation. Blood biomarker samples may be used for additional, exploratory analyses that may or may not be included in the CSR.

See Section 10.7 for information about access to blood biomarkers results.

Instructions for the collection, processing, storage, and shipment of blood biomarker samples will be provided in the Laboratory Manual.

11.3 Efficacy and Pharmacodynamics

11.3.1 Oral Glucose Tolerance Test

OGTT will be performed to assess 2-hour glucose levels. Depending on a subject's weight, 1.75 g/kg of body weight or 75 g maximum of oral glucose solution will be administered in the morning after at least 8 hours of fasting (except water and allowed medications other than prednisone and prednisolone). Investigators must counsel subjects on the safe withholding of insulins prior to each OGTT. Insulin use in the 24 hours prior to each OGTT will be recorded by the site.

Blood samples will be obtained at 0, 30 (±5), 60 (±5), 90 (±5), and 120 (±5) minutes after the start of ingestion of glucose solution. The 0-minute blood sample should be collected immediately prior to ingestion of glucose solution. During study visits with OGTTs, a blood sample will be collected post-OGTT to measure diabetes-related blood biomarkers, including insulin, C-peptide, glucagon, calculated indices of insulin secretion (insulinogenic index), and insulin resistance (HOMA-IR), and to measure incretin levels, including GLP-1 and GIP.

Specific instructions will be provided in the Laboratory Manual

11.3.2 Continuous Glucose Monitoring

CGM will be performed in subjects with CFRD only to assess dynamic, free-ranging changes in capillary glucose levels. A CGM sensor will be inserted subcutaneously by site medical staff, a home health nurse, or the subject after adequate training, calibrated, and worn for approximately 7 days (according to Table 3-2).

See Section 10.7 for information about access to CGM results.

11.3.3 Height and Weight

Height and weight will be measured with shoes off. Following screening, height will be collected only for subjects ≤21 years of age on the date of informed consent.

11.3.4 Insulin Use Diary

At each study visit, subjects who take insulin will provide the diary for documentation of insulin use for at least 7 days prior to the visit. Total daily dose of insulin will be recorded in the diary.

11.3.5 Sweat Chloride

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

11.4 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, and PEs, and ophthalmologic exams.

11.4.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with current ICH E6 GCP Guidelines. Section 13.1 outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting AEs.

11.4.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a local or central laboratory. As described below, urine pregnancy tests will either be analyzed by the site or at home using a home kit. All blood samples will be collected while subjects are in a seated or supine position. Specific instructions for the collection, processing, and shipment of samples will be provided in a separate Laboratory Manual.

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

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

Table 11-1 Safety Laboratory Test Panels

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

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

Pregnancy (β-human chorionic gonadotropin) Tests for all Female Subjects: All female subjects must have a serum pregnancy test at screening. Serum pregnancy tests will be performed at the by site medical staff or a home health nurse and analyzed at the central laboratory. Urine pregnancy tests will either be performed and analyzed at the site or at home by using a home kit provided by the site/home health nurse. Results will be reported to the site by telephone. The urine pregnancy test on Day 1 must be negative before the first dose of study drug is administered to the subject. Additional pregnancy tests may be required according to local regulations and/or requirements.

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

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

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

11.4.3 Physical Examinations and Vital Signs

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

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

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

Arterial oxygen saturation by pulse oximetry will be assessed following at least a 5-minute rest and before study drug dosing. Pulse oximetry will be collected before study drug dosing.

11.4.4 Electrocardiograms

Twelve-lead ECGs will be performed as indicated in Table 3-1 and Table 3-2. Additional 12-lead ECGs will be performed at any other time if clinically indicated. The performance of all ECGs will adhere to the following guidelines:

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

ECG traces will undergo safety review by the investigator and be maintained with source documentation. Clinically significant ECG abnormalities occurring during the study through the Safety Follow-up Visit will be recorded as AEs.

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

11.4.5 Ophthalmologic Examination

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

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

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

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

In addition to the screening ophthalmologic examination, subjects who are <18 years of age on the date of informed consent and who have completed at least 12 weeks of study drug treatment will have a single follow-up ophthalmologic examination. This examination should be completed at or up to 4 weeks before the Week 48 Visit, unless the subject prematurely discontinues study drug, in which case this examination should occur by the Safety Follow-up Visit (or ETT Visit for subjects who do not complete a Safety Follow-up Visit), as described in Table 3-2.

Any clinically significant abnormal findings will be reported as AEs.

11.4.6 Contraception and Pregnancy

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

11.4.6.1 Contraception

Contraception requirement for a couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. True abstinence must be practiced from the Screening Visit through 90 days after the last dose of study drug.
- If the male is infertile (e.g., bilateral orchiectomy). If a male subject is assumed to have complete bilateral absence of the vas deferens, infertility must be documented before the first dose of study drug (e.g., examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound).
- 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) will be considered to be of childbearing potential.
- Same-sex relationships

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

Table 11-2 Acceptable Methods of Contraception

	Male Subjects and Their Female (Non-study) Partners	Female Subjects and Their Male (Non-study) Partners
Vasectomy performed at least 6 months previously, with a documented negative postvasectomy semen analysis for sperm	Yes	Yes
Bilateral tubal occlusion (e.g., ligation) performed at least 6 months previously	Yes	Yes
Male or female condom with or without spermicide[a]	Yes	Yes
Female barrier contraception (such as diaphragm, cervical cap, or sponge) with spermicide	Yes	Yes
Continuous use of an intrauterine device for at least 90 days before the first dose of study drug	Yes	Yes
Oral, implanted, injected, or vaginal hormonal contraceptives, if successfully used for at least 60 days before the first dose of study drug	Yes	Yes

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

Additional notes:

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

11.4.6.2 Pregnancy

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

If a female subject becomes pregnant during study participation, study drug will be permanently discontinued immediately. The investigator will notify the medical monitor and Vertex 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 is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

12 STATISTICAL ANALYSIS

12.1 Sample Size and Power

The primary efficacy endpoint is change from baseline in 2-hour blood glucose levels following an OGTT to the average of Week 36 and Week 48. The primary null hypothesis to be tested is that the mean change from baseline in 2-hour blood glucose levels following OGTT to the average of Week 36 and Week 48 is equal to zero.

Assuming a within group SD of 45 mg/dL and a 10% dropout rate at Week 48, a sample size of 60 subjects will have more than 95% power to detect a mean decrease from baseline of -30 mg/dL in 2-hour blood glucose levels post-OGTT to the average of Week 36 and Week 48, based on a 2-sided, 1-sample *t*-test at a significance level of 0.05 using the EAST software Version 6.4.

12.2 Analysis Sets

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

The **All Subjects Set** will include all subjects who were enrolled. This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

The **Full Analysis Set** (FAS) is defined as all enrolled subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug. The FAS is to be used in efficacy analyses.

The **Safety Set** is defined as all subjects who have received at least 1 dose of study drug. The Safety Set is to be used for all safety analyses.

12.3 Statistical Analysis

This section presents a summary of the principal features of the planned statistical analyses. Statistical analysis details will be in the statistical analysis plan (SAP) which will be finalized before clinical database lock.

12.3.1 General Considerations

All individual subject data for subjects will be presented in individual subject data listings.

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

Categorical variables will be summarized using counts and percentages.

Baseline value, unless specified otherwise, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug. The baseline 2-hour blood glucose level from OGTT will be the average of measurements at screening and Day 1.

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

Relative change from baseline will be calculated and expressed in percentage as 100% × (Post-baseline value − Baseline value)/Baseline value.

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

Incomplete/missing data will not be imputed, unless specified otherwise.

12.3.2 Background Characteristics

Subject disposition, e.g., completed treatment, prematurely discontinued the treatment and the reason for discontinuation, will be summarized.

Demographic and baseline characteristics will be summarized.

Medications used will be coded using the World Health Organization-Drug Dictionary (WHO-DD) and summarized descriptively. Exposure to study drug in (i.e., duration of treatment) and dosing compliance (i.e., percentage of days being compliant to treatment) will be summarized descriptively.

Important protocol deviations will be provided in an individual subject data listing, and summarized, as appropriate.

Additional details will be provided in the SAP.

12.3.3 Efficacy and Pharmacodynamic Analysis

12.3.3.1 Analysis of Primary Efficacy Endpoint

The primary analysis will be based on a mixed-effects model for repeated measures (MMRM) with change from baseline in 2-hour post-OGTT blood glucose levels at Weeks 24, 36, and 48 as the dependent variable. The model will include visit as a fixed effect, and will be adjusted for main covariates as appropriate. The primary result obtained from the model will be the estimated mean change from baseline to the average of Week 36 and Week 48. The estimated change at each visit and the mean change to the average of Week 36 and Week 48 along with the 2-sided 95% CI and *P* value will be provided.

Additional details will be provided in the SAP.

12.3.3.2 Analysis of Secondary Efficacy Endpoints

The secondary endpoints include:

- Proportion of subjects with improvement in dysglycemia categorization (CFRD, IGT, NGT) at Week 48

The number and proportion of subjects with and without response at Week 48 defined as improvement in baseline dysglycemia categorization (i.e. CFRD at baseline to IGT/NGT based

on Week 48 OGTT measurement and IGT at baseline to NGT based on Week 48 OGTT measurement) will be presented. The 2-sided 95% Clopper-Pearson CI on the proportion of responders will also be presented.

Additional details will be provided in the SAP.

12.3.3.3 Multiplicity Adjustment

No multiplicity adjustment is planned.

12.3.3.4 Missing Data Handling

For the primary analysis of the primary endpoint, missing data will be assumed to be missing at random conditional on the observed data and covariate; consequently, no imputation of missing data will be performed.

12.3.3.5 Analysis of Other Efficacy Endpoints

Descriptive statistics will be provided for all other efficacy endpoints based on the FAS.

For the following endpoints, observed values and absolute change from baseline will be summarized:

- SwCl
- BMI
- Body weight
- HbA1c and fructosamine
- Insulin use (dose) in subjects using insulin
- Post-OGTT diabetes-related biomarkers (including insulin, C-peptide, glucagon, calculated indices of insulin secretion [insulinogenic index], and insulin resistance [HOMA-IR])
- Biomarkers of inflammation (including CRP)
- Biomarkers of pancreatic function (including FE-1 and serum IRT)
- Post-OGTT incretin levels (including GLP-1 and GIP)
- Percent of time spent in target blood glucose range of ≥70 to <140 mg/dL (≥3.89 to <7.77 mmol/L) as measured by 7-day CGM in subjects with CFRD
- Selected CGM parameters (including but not limited to percent of time spent between ≥140 and <200 mg/dL [≥7.77 and <11.10 mmol/L], percent of time spent ≥200 mg/dL [≥11.10 mmol/L], and MAGE) in subjects with CFRD

12.3.4 Safety Analysis

The overall safety profile will be assessed in terms of the following safety endpoints:

- Incidence of treatment emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., hematology, serum chemistry, coagulation, and urinalysis)
- 12-lead ECG outcomes

- Vital signs (including weight and height)
- Pulse oximetry

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

12.4 Interim Analysis

Not applicable

12.5 Data Monitoring Committee 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 subject completes study participation, as defined in Section 9.1.6

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

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

13.1.1.4 Adverse Event Severity

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

Table 13-1 Grading of AE Severity

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

Table 13-1 Grading of AE Severity

Classification	Description

Source: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed September 2019)
ADL: activities of daily living; AE: adverse event
Note: A semi-colon indicates 'or' within the description of the grade.
[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

13.1.1.5 Adverse Event Causality

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

Table 13-2 Classifications for AE Causality

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

AE: adverse event

13.1.1.6 Study Drug Action Taken

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

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

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

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

Classification[a]	Definition

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 global patient safety (GPS) **within 24 hours of identification**. In addition, all SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours of identification**.

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

Please send completed SAE Forms to Vertex GPS via:

Email: globalpatientsafety@vrtx.com (preferred choice)

Fax: +1-617-341-6159

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

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

13.1.2.3 Expedited Reporting and Investigator Safety Letters

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

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

13.2 Administrative Requirements

13.2.1 Product Complaints

A product complaint is defined as any verbal or written communication addressed to Vertex, or designee, of inquiry or dissatisfaction with the identity, strength, quality, or purity of a released drug product, IMP, or medical device. In addition, suspected counterfeit/falsified product is considered a product complaint.

Product complaints are to be reported to Vertex.

13.2.2 Ethical Considerations

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

13.2.3 Subject Information and Informed Consent

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

13.2.4 Investigator Compliance

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

When circumstances require an immediate departure from procedures set forth in the protocol, the investigator will contact Vertex to discuss the planned course of action. If possible, contact

will be made before the implementation of any changes. Any departures from the protocol will be fully documented in the source documentation and in a protocol deviation log.

13.2.5 Access to Records

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

13.2.6 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all 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.

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

13.2.7 Record Retention

The investigator will maintain all study records according to current ICH E6 GCP Guidelines and/or applicable local regulatory requirement(s), whichever is longest, as described in the Clinical Trial Agreement. If the investigator withdraws from the responsibility of keeping the study records, custody will be transferred to a person willing to accept the responsibility and Vertex will be notified.

13.2.8 Study Termination

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

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

- Subject or investigator noncompliance

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

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

13.2.9 End of Study

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

13.3 Data Quality Assurance

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

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

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

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

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

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

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

13.7.1 Publication of Study Results

Vertex is committed to reporting the design and results of all clinical studies in a complete, accurate, balanced, transparent, and timely manner, consistent with Good Publication Practices (GPP3).[19]

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

Authorship: Authorship of publications will be determined based on the Recommendations for Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states that authorship should be based on the following 4 criteria[20]:

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2. Drafting of the article or revising it critically for important intellectual content;
3. Final approval of the version to be published; and
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

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

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

13.7.2 Clinical Study Report

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

14 REFERENCES

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APPENDIX A Eligible MF *CFTR* Mutations

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

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

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

Inclusion of MF Mutations Based on In Vitro Testing

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

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

Eligible MF Mutations

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

This list does not include every eligible mutation, and investigators should contact the medical monitor regarding other mutations that may also meet study eligibility criteria.

Non-exhaustive List of Minimal Function *CFTR* Mutations Eligible for VX19-445-117

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

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

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

Non-exhaustive List of Minimal Function *CFTR* Mutations Eligible for VX19-445-117

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

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

CFTR: cystic fibrosis transmembrane conductance regulator gene

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

[a] Also known as 2183delAA>G.

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX19-445-117	Version #: 3.0	Version Date: 26 April 2021
Study Title: A Phase 3b Open-label Study to Assess the Effect of Elexacaftor/Tezacaftor/Ivacaftor on Glucose Tolerance in Cystic Fibrosis Subjects with Abnormal Glucose Metabolism		

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

[redacted]

15.2 Investigator Signature Page

Protocol #: VX19-445-117	Version #: 3.0	Version Date: 26 April 2021
Study Title: A Phase 3b Open-label Study to Assess the Effect of Elexacaftor/Tezacaftor/Ivacaftor on Glucose Tolerance in Cystic Fibrosis Subjects with Abnormal Glucose Metabolism		

I have read Protocol VX19-445-117, Version 3.0, and agree to conduct the study according to its terms. I understand that all information concerning elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date