1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3b Open-label Study Evaluating the Effects of Elexacaftor/Tezacaftor/Ivacaftor on Cough and Physical Activity in Cystic Fibrosis Subjects 12 Years of Age and Older Who Are Heterozygous for the *F508del* Mutation and a Minimal Function Mutation (F/MF)

Vertex Study Number: VX20-445-126

[redacted]

EudraCT Number: 2021-001628-16

Date of Protocol: 30 April 2021 (Version 1.0)

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2 PROTOCOL SYNOPSIS

Title A Phase 3b Open-label Study Evaluating the Effects of Elexacaftor/Tezacaftor/Ivacaftor on Cough and Physical Activity in Cystic Fibrosis Subjects 12 Years of Age and Older Who Are Heterozygous for the *F508del* Mutation and a Minimal Function Mutation (F/MF)

Brief Title A Study to Evaluate ELX/TEZ/IVA on Cough and Physical Activity in Subjects with Cystic Fibrosis (CF)

Clinical Phase and Clinical Study Type Phase 3b, investigation of cough and physical activity

Objective To evaluate the effects of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) on cough and physical activity using wearable technology

Endpoints

Primary Endpoint

Percent reduction from baseline in cough frequency (cough events per day) to the average of Week 8 through Week 12

Secondary Endpoint

Absolute change from baseline in total step count per day to the average of Week 8 through Week 12

[redacted]

Number of Subjects Approximately 100 subjects will be enrolled

Study Population Male and female subjects with CF who are 12 years of age or older, heterozygous for the *F508del* mutation and a minimal function (MF) mutation (F/MF genotypes), and CFTR modulator naïve (none allowed within 6 months before Day -14)

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)

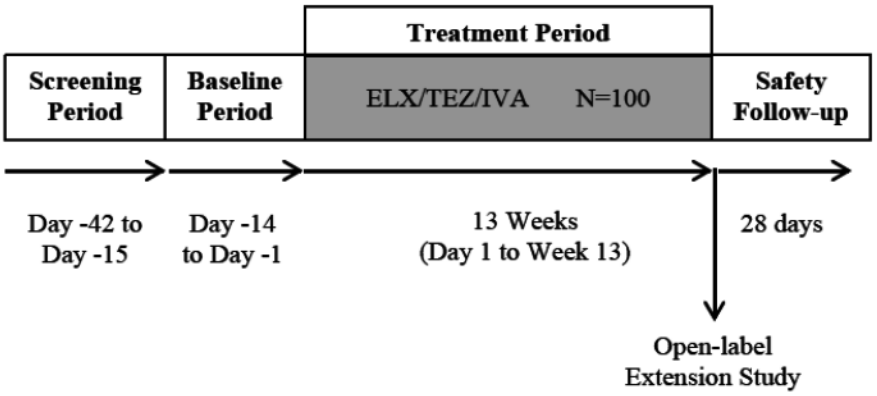
Activity: CFTR potentiator

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

Study Duration Excluding the Screening Period, the total study duration is approximately 19 weeks (2 weeks for the Baseline Period, approximately 13 weeks for the Treatment Period, and approximately 4 weeks for the Safety Follow-up Period).

Study Design This is a Phase 3b, open-label study of cough and physical activity in CF subjects 12 years of age and older with F/MF genotypes. A 2-week baseline period will be used to establish baseline cough and activity patterns prior to the first dose of study drug. A schematic of the study design is shown in Figure 2-1.

Figure 2-1 VX20-445-126 Study Design



ELX: elexacaftor; IVA: ivacaftor; N: total sample size; TEZ: tezacaftor

Notes: Subjects who are eligible 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 13 Visit and have enrolled in the open-label extension study, or who transition to a commercially available CFTR modulator regimen, 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:

- Cough measurements via cough monitoring system
- Activity [redacted] measurements via wrist-worn actigraphy sensor

Safety: AEs, clinical laboratory assessments [redacted] physical examinations, [redacted] (for subjects <18 years of age on the date of informed consent)

[redacted]

Statistical Analyses

The primary efficacy endpoint is percent reduction from baseline in cough frequency (cough events per day) to the average of Week 8 through Week 12.

Assuming a standard deviation of 1 for the log ratio of cough frequency post-baseline versus baseline, a sample size of approximately 100 subjects will provide a reasonable precision for the estimation of percent reduction from baseline in cough frequency, after accounting for 20% missing. Note that percent reduction equals 100% × (1-ratio of cough frequency post-baseline versus baseline).

The primary efficacy analysis will be based on a mixed-effects model for repeated measures (MMRM).

The safety analyses will be descriptive only.

3 SCHEDULE OF ASSESSMENTS

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

Table 3-1 Study VX20-445-126: Screening

Event/Assessment	Screening Visit Day -42 to Day -15	Comments
Study visit	X	The Screening Visit must be performed in the clinic.
Informed consent (and assent, if applicable)	X	Electronic consent may be used, as applicable, if permitted by local regulations. If not permitted or if subject declines electronic consent, subjects will sign a paper consent form.
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 11.1)
[redacted]		
Complete PE	X	Section 11.4.3
[redacted]		
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 and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).
FSH	X	Performed for any suspected menopausal female with at least 12 months of continuous spontaneous amenorrhea (Section 11.4.2)
Serum pregnancy (all female subjects)	X	Section 11.4.2
Serum chemistry (including creatine kinase)	X	
Hematology	X	
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.

FSH: follicle stimulating hormone; PE: physical examination

Table 3-2 Study VX20-445-126: Baseline Period, Treatment Period, and Safety Follow-up Visit

Event/Assessment[a]	Baseline Period	Treatment Period						ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)[b]	Comments
	Day -14 to Day -1	Day 1	Weeks 2, 3, 5, 6, 7, 9, 10, 11	Week 4	Week 8	Week 12	Week 13			
Study visit		X					X (+6 days[c])	X	X	Must be performed in the clinic.
Telemedicine contact	Day -14, Day -7 (+6 days[c])		X (+6 days[c])	X (+6 days[c])	X (+6 days[c])	X (+6 days[c])				Assess subject's status, any AEs, concomitant medications, treatments, procedures, results of the urine pregnancy test (all female subjects), study drug count, and observe subject placement of cough device.
Safety, Efficacy, and Other Assessments										
[redacted]										
Complete PE		X					X	X		Section 11.4.3
[redacted]										
Height and weight		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 11.1)

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

[b] The Safety Follow-up Visit is not required for subjects who complete the Week 13 Visit and have enrolled in an open-label extension study, or who transition to a commercially available CFTR modulator regimen, within 28 days after the last dose of study drug.

[c] The 7-day window begins on the first day of that week (e.g., at Week 2 the window begins on Day 8, at Week 3 the window begins on Day 15, etc.).

Table 3-2 Study VX20-445-126: Baseline Period, Treatment Period, and Safety Follow-up Visit

Event/Assessment[a]	Baseline Period	Treatment Period						ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)[b]	Comments
	Day -14 to Day -1	Day 1	Weeks 2, 3, 5, 6, 7, 9, 10, 11	Week 4	Week 8	Week 12	Week 13			
[redacted]										
Pregnancy test (all female subjects)		Urine		Urine	Urine	Urine		Urine	Urine	During the Treatment Period, a urine pregnancy test will be performed with a home kit provided by the study site. Results will be reported to the site (Section 11.4.2).
Serum chemistry		X					X	X	X	Section 11.4.2
[redacted]										

Table 3-2 Study VX20-445-126: Baseline Period, Treatment Period, and Safety Follow-up Visit

Event/Assessment[a]	Baseline Period	Treatment Period						ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)[b]	Comments
	Day -14 to Day -1	Day 1	Weeks 2, 3, 5, 6, 7, 9, 10, 11	Week 4	Week 8	Week 12	Week 13			
Cough measurements	Day -14, Day -7		X	X	X	X				Cough monitoring system will be used for a single day (defined by 24 continuous hours) at each time point (Section 11.2.1). Subjects will put the cough device on under direct observation at the time of contact between the subject and investigator or site personnel (i.e., in person or telemedicine contact).
Activity measurements	Continuous from Day -14 through Week 13 Visit									Wrist-worn actigraphy sensor will be worn 24 hours per day during the Baseline Period and Treatment Period (Section 11.2.2).
[redacted]										
Adverse events	Continuous from date of informed consent through completion of study participation									Completion of study participation is defined in Section 9.1.6.
Medications review	Continuous from date of informed consent through completion of study participation									
Treatment and procedures review	Continuous from date of informed consent through completion of study participation									

Table 3-2 Study VX20-445-126: Baseline Period, Treatment Period, and Safety Follow-up Visit

Event/Assessment[a]	Baseline Period	Treatment Period						ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)[b]	Comments
	Day -14 to Day -1	Day 1	Weeks 2, 3, 5, 6, 7, 9, 10, 11	Week 4	Week 8	Week 12	Week 13			
Study Drug Administration										
Study drug dosing		ELX/TEZ/IVA Day 1 through evening before Week 13 Visit								Administered within approximately 30 minutes of consuming fat-containing food (e.g., standard "CF" meal or snack) (Section 9.6.1). At the Day 1 Visit, the morning dose of study drug will be administered under the supervision of qualified personnel after predose assessments have been completed.
Study drug count		X		X	X	X	X	X		At consultation between the subject and investigator (i.e., in person or telemedicine contact), study drug compliance will be assessed.

AEs: adverse events; CF: cystic fibrosis; [redacted]; ELX: elexacaftor; ETT: Early Termination of Treatment; [redacted]; IVA: ivacaftor; PE: physical examination; [redacted] TEZ: tezacaftor

4 TABLE OF CONTENTS

List of Tables

List of Figures

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
[redacted]	
CD	compact disc
CF	Cystic Fibrosis
[redacted]	
CFTR	CF transmembrane conductance regulator protein
CFTR	CF transmembrane conductance regulator gene
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
[redacted]	
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
ELX	elexacaftor
[redacted]	
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
$FEF_{25\%-75\%}$	forced expiratory flow, midexpiratory phase
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLI	Global Lung Function Initiative
GPP3	Good Publication Practice
GPS	Global Patient Safety
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee

Abbreviation	Definition
IMP	investigational medicinal product
IND	Investigational New Drug (application) (US)
IRB	institutional review board
IVA	ivacaftor
IWRS	interactive web response system
LUM	lumacaftor
max	maximum value
[redacted]	
MF	minimal function
min	minimum value
MMRM	mixed-effects model for repeated measures
[redacted]	
P	probability
PC	publication committee
PE	physical examination
P-gp	P-glycoprotein
PI	principal investigator
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
[redacted]	
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
SUSARs	serious adverse reactions
TE	Treatment-emergent
TEAEs	treatment emergent adverse events
TEZ	tezacaftor
ULN	upper limit of normal
US	United States

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 80,000 individuals worldwide (approximately 31,000 in the US and 49,000 in the EU).[1-4]

CF is caused by decreased quantity and/or function of the CFTR protein due to mutations in the *CFTR* gene.[5] 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.[6] Despite progress in the treatment of CF with symptomatic therapies, 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.[1, 2] More effective treatments are needed for CF.

The most common disease-causing mutation is *F508del*: approximately 85.3% of people with CF in the US and 80.6% in Europe have at least one *F508del* allele.[1, 2]

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.[7, 8] The clinical testing and regulatory approval of CFTR modulators in certain countries for the treatment of people with CF caused by specific *CFTR* genotypes have 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 (Trikafta™, Kaftrio™).

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

Wearable technologies can provide valuable information on a subject's cough frequency, physical activity, [redacted] in a real-world setting; however, these technologies have not been widely used in the CF population, especially in those on highly effective CFTR modulator therapy. The purpose of this study is to evaluate the effect of ELX/TEZ/IVA on cough and physical activity using wearable technology in CF subjects heterozygous for *F508del* and a second *CFTR* allele carrying a minimal function (MF) mutation that is not responsive to IVA or TEZ/IVA (F/MF genotypes).

6 STUDY OBJECTIVE

To evaluate the effects of ELX/TEZ/IVA on cough and physical activity using wearable technology

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Percent reduction from baseline in cough frequency (cough events per day) to the average of Week 8 through Week 12

7.2 Secondary Endpoint

Absolute change from baseline in total step count per day to the average of Week 8 through

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% and ≤90% 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.

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 (or on a transplant list)
   - 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)
   - Non-ambulatory status
2. Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject (as deemed by the investigator).
3. Any of the following abnormal laboratory values at screening:
   - Hemoglobin <10 g/dL
   - Total bilirubin ≥2 × upper limit of normal (ULN)

- Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN
- Abnormal renal function defined as glomerular filtration rate ≤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.

4. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug).
5. Lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For subjects who have had a history of a positive culture, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
   - The subject has not had a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent.
   - The subject has had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent.
6. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug (Day 1).
7. Ongoing or prior participation in an investigational drug study within 28 days of the Screening Visit.
   - A washout period of 5 terminal half-lives of the previous investigational study drug, or 28 days, whichever is longer, must elapse before the Screening Visit.
   - The duration of the elapsed time may be longer if required by local regulations.
8. Use of restricted medication within specified duration before the first dose of study drug as defined in Table 9-1.
9. Pregnant and breast-feeding females. All female subjects regardless of childbearing potential (Section 11.4.6) must have a negative pregnancy test at the Screening Visit and the Day 1 Visit.
10. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site. 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.

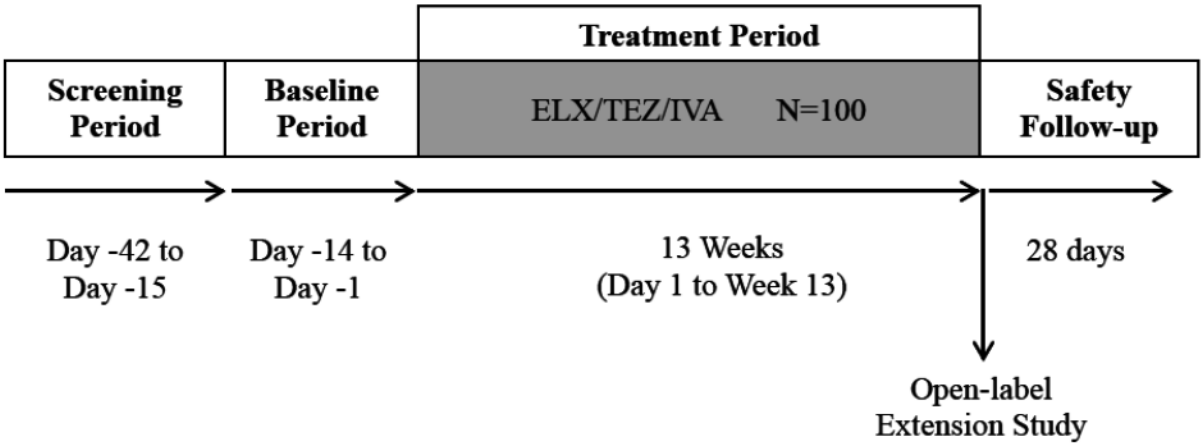
9 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 3b, open-label study of cough and physical activity in CF subjects 12 years of age and older with F/MF genotypes. A 2-week baseline period will be used to establish baseline cough and activity patterns prior to the first dose of study drug. A schematic of the study design is shown in Figure 9-1.

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

Figure 9-1 VX20-445-126 Study Design



ELX: elexacaftor; IVA: ivacaftor; N: total sample size; TEZ: tezacaftor

Notes: Subjects who are eligible 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 13 Visit and have enrolled in the open-label extension study, or who transition to a commercially available CFTR modulator regimen, 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 between Day -42 and Day -15. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from each subject, as specified in Table 3-1.

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

9.1.1.1 Repetition of Screening Assessment(s)

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

9.1.1.2 Rescreening

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

- *CFTR* genotyping
- Follicle-stimulating hormone (FSH) level (if serum FSH level was in the postmenopausal range as determined by the laboratory performing the test during prior screening)
- 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 13 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 13 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.

Wearable devices must be returned to the site during the ETT Visit.

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

9.1.6 Completion of Study Participation

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

- For subjects who complete the Treatment Period and enter an open-label extension safety study within 28 days of the Week 13 Visit: the Week 13 Visit
- For subjects who complete the Treatment Period and do not enter an open-label extension safety study within 28 days of the Week 13 Visit: the Safety Follow-up Visit
- For subjects who prematurely discontinue study drug treatment but do not withdraw consent (and assent, as applicable): the later 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

Study visits must be performed in the clinic as specified in Table 3-1 and Table 3-2. A number of other contacts will be performed remotely via telemedicine contact. Under extenuating circumstances, certain remote measures may be implemented (e.g., due to safety concerns and/or local restrictions related to COVID-19 or other emerging events). Even under extenuating circumstances, the Screening (including initial consent), Day 1, Week 13, ETT, and Safety Follow-up 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.

- Study drug may be shipped directly from the site to the subject, as applicable and as allowed per local regulations.
- Remote monitoring visits may be implemented, as applicable (including remote source data verification) and as allowed per local regulations.

9.2 Method of Assigning Subjects to Treatment Groups

This is an open-label study.

9.3 Rationale for Study Elements

9.3.1 Study Design

This open-label study will evaluate the effects of ELX/TEZ/IVA on cough and physical activity in CF subjects. Wearable technology will be used to measure cough frequency, daily physical

activity, [redacted] in a real-world setting. A 2-week baseline period will be used to establish baseline cough, activity, [redacted] prior to the first dose of study drug.

9.3.2 Study Population

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

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 sweat chloride (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.

The cough, physical activity, [redacted] will be performed using wearable technology. These measurements will help to inform on the effects of ELX/TEZ/IVA on cough, physical activity, [redacted] in a real-world setting.

Cough is one of the most common and burdensome symptoms of CF and negatively impacts quality of life. The measurement of cough frequency reduction in response to treatment with ELX/TEZ/IVA would be a clinically meaningful outcome measure. The cough monitoring system is a reliable, robust, and efficient tool for the objective measurement of cough frequency. Using mechanoacoustic measurements, cough counts can be obtained over a continuous 24-hour period.

Daily activity [redacted] reflect both the functional and physiological health of subjects. Use of a well-validated Class I actigraphy medical device would allow for the collection of quantifiable metrics around daily activity [redacted]. In conjunction with subject-reported data (activity and cough diary, [redacted]), the actigraphy data will enable the potential health economic impact of ELX/TEZ/IVA. Actigraphy devices are worn on the wrist and provide objective information on physical activity [redacted] habits in the patient's natural environment. The actigraphy device is a cost-effective and minimally invasive in-home alternative to other methods to measure these behaviors (e.g., polysomnography), and offers a level of accuracy and reliability that cannot be achieved through subjective patient reports.

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 6 months before Day -14	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.
- ELX may inhibit OATP1B1 and OATP1B3, which may increase the exposure of medicinal products that are substrates for these transporters. Substrates such as statins, glyburide, nateglinide, and repaglinide should be used with caution.
- IVA is a weak inhibitor of P-glycoprotein (P-gp). Administration of IVA may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. Digoxin or other substrates of P-gp with a narrow therapeutic index, such as cyclosporine, everolimus, sirolimus, and tacrolimus, should be used with caution and appropriate monitoring.
- IVA may inhibit CYP2C9; therefore, during coadministration with warfarin, additional monitoring of the international normalized ratio is recommended. Other medicinal products that are CYP2C9 substrates for which exposure may be increased include glimepiride and glipizide; these should be used with caution.
- Information about bronchodilator use during the study will be collected and documented. Subjects who are using a bronchodilator should have their spirometry assessments performed according to the guidelines provided in Section 11.3.4.

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 (e.g., 2 ELX/TEZ/IVA fixed-dose combination [FDC] tablets in the morning and 1 IVA tablet in the evening). Additional information is provided in the Pharmacy Manual.

Study drug should be administered with a fat-containing meal or snack, such as a standard “CF” meal or snack or a standard meal 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 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. At the Day 1 Visit, the morning dose of study drug will be administered under the supervision of site medical staff after predose assessments have been completed. The meal or snack will be provided by the site on Day 1 for the morning dose of study drug.

5. Study drug will be dispensed at the Day 1 Visit. Subjects will be instructed to return all used and unused study drug to the site at the Week 13 Visit.
6. At the Week 13 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 13 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 an ETT Visit and Safety Follow-up Visit, if applicable (see Section 9.1.4), and follow up with the subject regarding any unresolved AEs.

If 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 Baseline Period or 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. Subjects will be instructed to return all used and unused materials associated with the study drug to the site. These materials will be retained at the site according to instructions provided by Vertex or its designee. The study monitor will review study drug records and inventory throughout the study.

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

10.5 Disposal, Return, or Retention of Unused Drug

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

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

10.6 Compliance

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

If a subject or 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 [redacted] cough, activity, [redacted] 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 (Section 8). The medical history will include a complete review of systems, medical and surgical histories, and any allergies.

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.

11.2 Efficacy

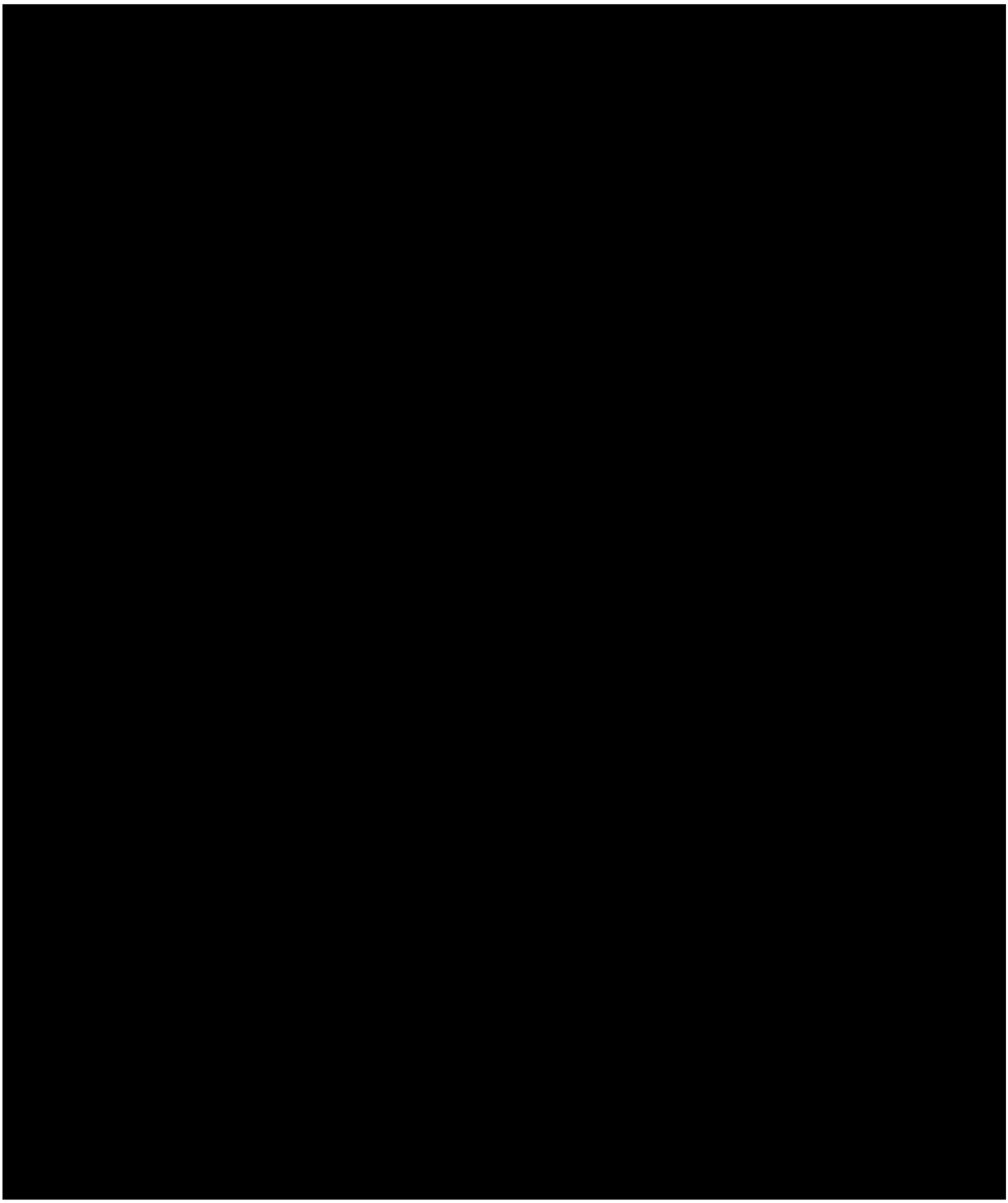
11.2.1 Cough Measurements

Subjects will be provided with a non-invasive, semi-automated, ambulatory cough monitoring system to record cough frequency. The system will be used for a single day (defined by 24 continuous hours) at time points specified in Table 3-2. Subjects will put the cough device on under direct observation at the time of contact between the subject and investigator or site personnel (i.e., in person or telemedicine contact).

11.2.2 Activity Measurements

Subjects will be provided with a wrist-worn actigraphy sensor (similar to a watch) to measure behavioral outcomes (e.g., step count, cadence, time spent in physical activity intensity categories, [redacted] etc.). The wrist-worn device will be worn 24 hours per day during the Baseline Period and the Treatment Period (except for pre-specified charging time points) and will be returned to the study site upon completion of the study (Section 9.1.6).

[redacted]



[redacted]

11.4 Safety

Safety evaluations will include AEs, clinical laboratory assessments, physical examinations, [redacted] for subjects <18 years of age on the date of informed consent).

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

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[a]
Glucose	Hemoglobin
Blood urea nitrogen[b]	Erythrocytes
Creatinine	Mean corpuscular volume
Sodium	Platelets
Potassium	Reticulocytes
Calcium	Leukocytes
Chloride	Differential (absolute and percent):
Magnesium	Eosinophils
Bicarbonate	Basophils
Phosphate	Neutrophils
Total bilirubin, direct bilirubin, indirect bilirubin	Lymphocytes
Alkaline phosphatase	Monocytes
Aspartate transaminase	
Alanine transaminase	
Amylase	
Lipase	
Gamma-glutamyl transferase	
Protein	
Albumin	
Creatine kinase[c]	
Cholesterol	

[a] Hematology will only be performed at screening.
[b] If blood urea nitrogen cannot be collected, urea may be substituted.
[c] Creatine kinase measured at screening only.

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 by site medical staff and analyzed at the central laboratory. Urine pregnancy tests will either be performed and analyzed at the site or at home by using a home kit provided by the site. Results will be reported to the site by telemedicine contact. The urine pregnancy test on Day 1 must be negative before the first dose of study drug is administered to the subject. Additional pregnancy tests may be required according to local regulations and/or requirements.

FSH (Screening Period only): Blood samples for FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea (Section 11.4.6.1). Serum FSH levels must be in the postmenopausal range as determined by the laboratory performing the test.

CF genotype (Screening Period only): A valid previous *CFTR* genotype laboratory report may be used to establish eligibility. If subjects cannot provide a valid previous *CFTR* genotype laboratory report at screening, central laboratory 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 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.

[redacted]

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 Global Patient Safety (GPS) within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form. Male subjects with female partners who become pregnant during the study must use a male condom to avoid exposure of a potential embryo or fetus to study drug via the seminal fluid.

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

Approximately 100 subjects will be enrolled.

The primary efficacy endpoint is percent reduction from baseline in cough frequency (cough events per day) to the average of Week 8 through Week 12. Assuming a standard deviation of 1 for the log ratio of cough frequency post-baseline versus baseline, a sample size of approximately 100 subjects will provide 95% confidence intervals (which represents the estimation precision) as shown in Table 12-1 at various observed percent reductions in cough frequency (30%, 40%, and 50%), after accounting for 20% missing. Note that percent reduction equals 100% × (1-ratio of cough frequency post-baseline versus baseline).

Table 12-1 95% Confidence Intervals for Percent Reduction in Cough Frequency per Day From Baseline

Percent reduction in cough frequency	30%	40%	50%
95% Confidence Intervals	(13%, 44%)	(25%, 52%)	(38%, 60%)

Note: 30%, 40%, and 50% percent reduction corresponds to ratio of 0.7, 0.6, and 0.5 in cough frequency (post-baseline vs. baseline), respectively.

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 **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

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

Categorical variables will be summarized using counts and percentages.

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

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

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., enrolled, completed treatment, prematurely discontinued treatment, and entered an open-label extension) will be summarized based on the All Subjects Set.

Demographics and baseline characteristics will be summarized. Also, medical history and medication use will be 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 Analysis

12.3.3.1 Analysis of Primary Endpoint

The primary endpoint is percent reduction from baseline in cough frequency (cough events per day) to the average of Week 8 through Week 12. The primary analysis will be based on a mixed-effects model for repeated measures (MMRM) with change from baseline at each post-baseline visit on the natural log scale as the dependent variable. The model will include week as fixed effects and baseline cough frequency as covariate.

The primary result obtained from the model will be the estimated percent reduction in cough frequency from baseline to the average of Week 8 through Week 12, i.e., 100% × (1-exponential form of LS mean change estimate from the above MMRM model). The 2-sided 95% confidence intervals will be provided. Furthermore, the estimated percent reduction at each post-baseline week will also be provided.

Additional details will be provided in the SAP.

12.3.3.2 Analysis of Secondary Endpoint

The secondary endpoint is absolute change from baseline in total step count per day to the average of Week 8 through Week 12.

For total step counts per day, the baseline value is defined the average of total step count per day in a 7-day period prior to first dose of study drug. The treatment period will be divided into 12 weekly intervals (Week 1, Week 2, ... Week 12), and the average of total step count per day will be calculated for each weekly interval. The analysis will be based on a MMRM model with change from baseline at each post-baseline weekly interval as the dependent variable. The model will include week as fixed effects and baseline total step count per day as covariate.

The primary result obtained from the model will be the estimated mean change from baseline to the average of Week 8 through Week 12. The 2-sided 95% confidence intervals will be provided. Furthermore, the estimated mean change at each post-baseline weekly interval will also be provided.

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.

[redacted]

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

[redacted]

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

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

13.1.1.4 Adverse Event Severity

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

Table 13-1 Grading of AE Severity

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

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

13.1.1.5 Adverse Event Causality

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

Table 13-2 Classifications for AE Causality

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

Table 13-2 Classifications for AE Causality

Classification	Definition

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.

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

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

follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

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

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

13.1.2.3 Expedited Reporting and Investigator Safety Letters

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

13.2.7 Record Retention

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

study records, custody will be transferred to a person willing to accept the responsibility and Vertex will be notified.

13.2.8 Study Termination

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

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

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

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

13.2.9 End of Study

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

13.3 Data Quality Assurance

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

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

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

13.4 Monitoring

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

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

13.5 Electronic Data Capture

Vertex will provide the study sites with secure access to and training on the EDC and decentralized trial platform applications 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. Additionally, subjects will use the decentralized trial platform to record electronic activity and cough diary, [redacted] which will be considered the source for that data.

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.

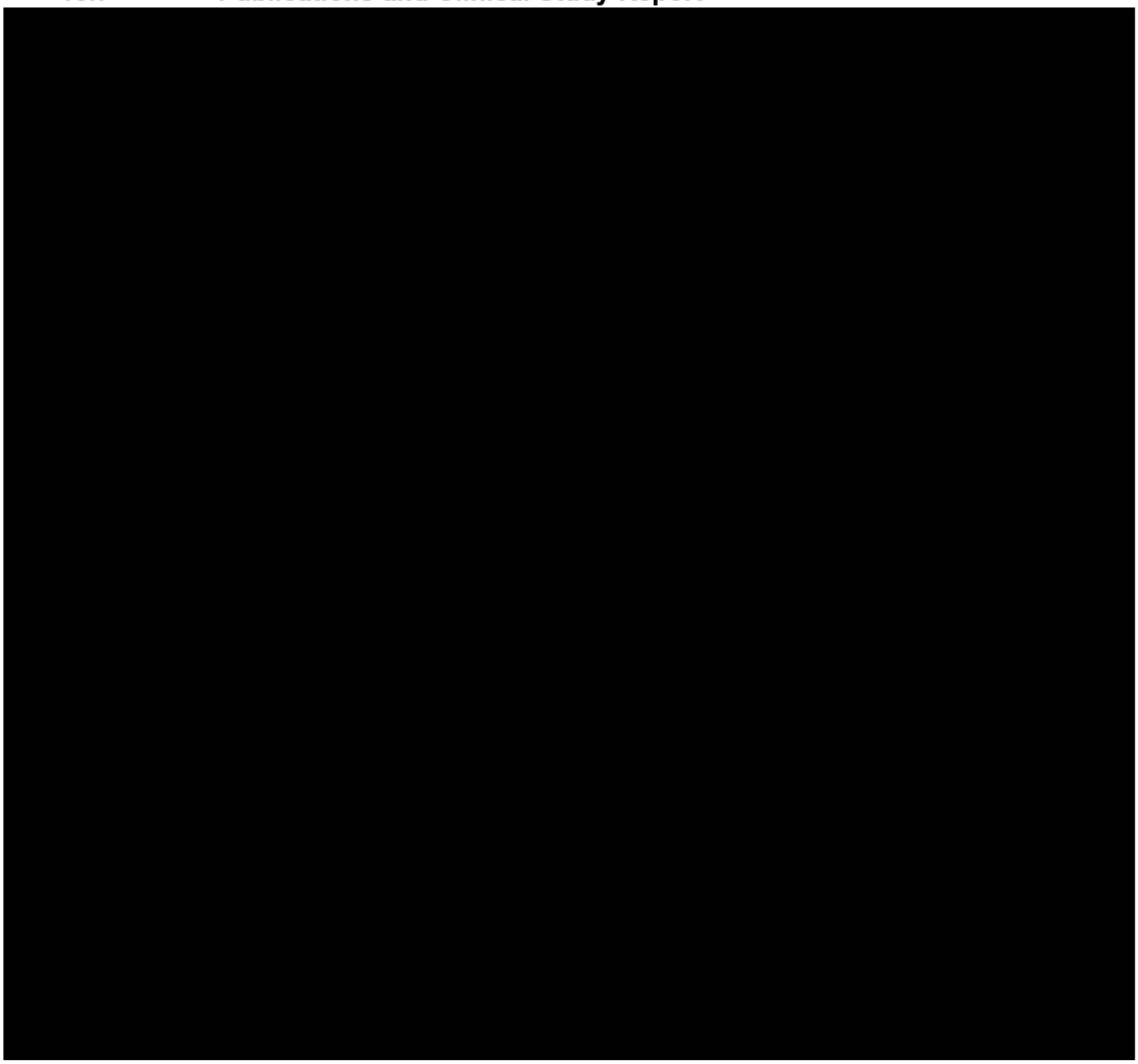
13.6 Confidentiality and Disclosure

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



13.7.2 Clinical Study Report

A clinical study report (CSR), written in accordance with the current ICH E3 Guideline, will be submitted in accordance with local regulations.

14 REFERENCES

1 Cystic Fibrosis Foundation. 2019 Patient Registry Annual Data Report. Bethesda, MD: 2020.

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APPENDIX A Eligible MF *CFTR* Mutations

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

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

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

Inclusion of MF Mutations Based on In Vitro Testing

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

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

Eligible MF Mutations

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

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

Non-exhaustive List of Minimal Function *CFTR* Mutations Eligible for VX20-445-126

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

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

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

Non-exhaustive List of Minimal Function *CFTR* Mutations Eligible for VX20-445-126

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 #: VX20-445-126	Version #: 1.0	Version Date: 30 April 2021
Study Title: A Phase 3b Open-label Study Evaluating the Effects of Elexacaftor/Tezacaftor/Ivacaftor on Cough and Physical Activity in Cystic Fibrosis Subjects 12 Years of Age and Older Who Are Heterozygous for the *F508del* Mutation and a Minimal Function Mutation (F/MF)		

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

Printed Name	Title
Signature	Date

15.2 Investigator Signature Page

Protocol #: VX20-445-126	Version #: 1.0	Version Date: 30 April 2021
Study Title: A Phase 3b Open-label Study Evaluating the Effects of Elexacaftor/Tezacaftor/Ivacaftor on Cough and Physical Activity in Cystic Fibrosis Subjects 12 Years of Age and Older Who Are Heterozygous for the *F508del* Mutation and a Minimal Function Mutation (F/MF)		

I have read Protocol VX20-445-126, Version 1.0, and agree to conduct the study according to its terms. I understand that all information concerning elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date