1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy of Ivacaftor in Subjects with Cystic Fibrosis Who are 6 Years of Age and Older and Have Either a 3849 + 10KB C→T or D1152H-CFTR Mutation

Vertex Study Number: VX16-770-127

Date of Protocol: 20 October 2016 (Version 1.0)

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

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2 PROTOCOL SYNOPSIS

Title A Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy of Ivacaftor in Subjects with Cystic Fibrosis Who are 6 Years of Age and Older and Have Either a 3849 + 10KB C→T or D1152H-CFTR Mutation

Brief Title A Study to Evaluate Efficacy of Ivacaftor in Subjects With Cystic Fibrosis Who Have a *3849 + 10KB C→T* or *D1152H CFTR* Mutation

Clinical Phase and Clinical Study Type Phase 3b, efficacy

Objectives

Primary:

To evaluate the efficacy of ivacaftor treatment in subjects with cystic fibrosis (CF) 6 years of age and older who have a *3849 + 10KB C→T* or *D1152H* CF transmembrane conductance regulator gene *(CFTR)* mutation.

[redacted]

Endpoints

Primary:

Change from baseline in lung clearance index$_{2.5}$ ($LCI_{2.5}$; calculated as lung volume turnovers required to reach 2.5% of the starting nitrogen [N_2] concentration) through 8 weeks of treatment

[redacted]

Number of Subjects Approximately 50 subjects

Study Population Male or female subjects 6 years of age and older weighing ≥25 kg who have CF and a *3849 + 10KB C→T* or *D1152H CFTR* mutation on at least 1 allele.

Investigational Drug

Active substance: ivacaftor

Activity: CFTR potentiator

Strength and route of administration: 150 mg film-coated tablets for oral administration.

Study Duration Excluding the Screening Period, each subject will participate in the study for approximately 28 weeks (Day 1 through the Safety Follow-up Visit).

Study Design This study is a randomized, double-blind, placebo-controlled, single-center, crossover, exploratory study.

The crossover design includes two 8-week treatment periods separated by an 8-week (±4 days) washout period. Subjects will be randomized to receive Ivacaftor, 150 mg every 12 hours (q12h), in Treatment Period 1 and placebo in Treatment Period 2, or placebo in Treatment Period 1 and ivacaftor (150 mg q12h) in Treatment Period 2.

Assessments Efficacy:

Multiple breath washout (MBW); [redacted]

Safety:

Adverse events (AEs), clinical laboratory assessments (amylase, lipase, and liver function tests [LFTs]), physical examinations and vital signs, and ophthalmological examinations (OEs) (for subjects <18 years of age) [redacted]

Statistical Analyses No formal sample size calculation was conducted. The planned sample size of approximately 50 subjects is based on the number of subjects expected to be available for participation in this study.

The Full Analysis Set (FAS) is defined as all randomized subjects who have received at least 1 dose of study drug. The FAS will be used for efficacy analyses.

The Safety Set is defined as all enrolled subjects who received at least 1 dose of study drug. The Safety Set will be used for safety analyses. Study baseline is defined as the most recent nonmissing measurement collected before the first administration of study drug in Treatment Period 1; and all the statistical inferences will be based on change from study baseline.

Efficacy:

Bayesian analyses will be used to estimate the effect of ivacaftor versus placebo on $LCI_{2.5}$. A non-informative prior distribution (normal distribution with mean 0 and variance = 10^6) on the treatment difference will be assumed. The posterior distribution of the treatment difference will be obtained using the Markov Chain Monte Carlo (MCMC) method.

Supportive analyses of change from study baseline through 8 weeks of ivacaftor treatment versus placebo in $LCI_{2.5}$ will be performed based on a mixed-effects model for repeated measures (MMRM).

[redacted]

Safety:

The incidence of treatment-emergent AEs (TEAEs) will be summarized in contingency tables (n, percentage) by treatment. For other safety parameters (e.g., vital signs), the raw values and changes from baseline will be summarized

by treatment. Additionally, all safety data will be presented in subject data listings.

3 SCHEDULE OF ASSESSMENTS

Schedules of Assessments are shown in Table 3-1 and Table 3-2.

Table 3-1 Study VX16-770-127: Screening Period Assessments

Event/Assessment	Screening Period (Day -28 through Day-1)
Informed consent form (ICF) and assent form (when applicable)	X
Review inclusion/exclusion criteria	X
Demographics	X
Medical history (includes CF genotype)	X
Prior and concomitant medications	X
Ophthalmological history	X
Ophthalmologic examination[a]	X
Physical examination	X
Weight and height[b]	X
Vital signs[c]	X
Multiple breath washout[d]	X
Spirometry[d]	X
Sweat chloride	X
[redacted]	
Serum follicle-stimulating hormone (FSH; suspected postmenopausal female subjects only)[e]	X
Serum pregnancy test (female subjects of childbearing potential)[f]	X
Hematology	X
Serum chemistry	X
Adverse events	Continuous from signing of the ICF and Assent (where applicable) through the Safety Follow-up Visit

[a] OE is required for subjects who are under 18 years of age at the Screening Visit. If there is documentation of an OE that met protocol criteria and was conducted within 3 months before the Screening Visit, the subject is not required to have another OE during Screening.

[b] Weight and height will be measured with shoes off.

[c] Vital signs (blood pressure, pulse rate, respiration rate, and body temperature) will be collected after the subject has been at rest (supine) for 5 minutes. Vital sign assessments will be performed before blood draws.

[d] At Screening, spirometry and MBW may be performed pre- or post-bronchodilator.

[e] FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be ≥40 mIU/mL to be considered postmenopausal.

[f] See Section 11.5.6.1 for definition of childbearing potential.

Table 3-2 Study VX16-770-127: Treatment Period and Follow-up Visit Assessments

Event/Assessment	Treatment Period 1			Washout Period	Treatment Period 2			Early Termination of Treatment (ETT)	Safety Follow-up 4 weeks (± 7 days) after last dose of study drug[a]
	Day 1	Week 4 (± 4 days)	Week 8 (± 4 days)	8 weeks (± 4 days)	Day 1	Week 4 (± 4 days)	Week 8 (± 4 days)		
Review of inclusion /exclusion criteria	X								
Randomization	X								
[redacted]									
Meal(s) or snack(s) at site[c]	X	X	X		X	X	X		
Vital signs[d]	X	X	X		X	X	X	X	X
[redacted]									
Physical examination	X		X		X		X	X	X
Multiple breath washout[f]	X	X	X		X	X	X		
[redacted]									

[a] If the ETT Visit occurs >3 weeks after the last dose of study drug, the Follow-up Visit will not be required.

[redacted]

[c] Fat-containing food such as a standard CF high-fat, high-calorie meal or snack will be provided to subjects at the site after all predose assessments have occurred.

[d] Vital signs (blood pressure, pulse rate, respiration rate, and body temperature) will be collected after the subject has been at rest (supine) for 5 minutes. Blood pressure will be measured by sphygmomanometer. Vital sign assessments will be performed before blood draws.

[redacted]

[f] Multiple breath washout [redacted] will be performed pre-bronchodilator [redacted], and must be performed before dosing.

[redacted]

Table 3-2 Study VX16-770-127: Treatment Period and Follow-up Visit Assessments

Event/Assessment	Treatment Period 1			Washout Period	Treatment Period 2			Early Termination of Treatment (ETT)	Safety Follow-up 4 weeks (± 7 days) after last dose of study drug[a]
	Day 1	Week 4 (± 4 days)	Week 8 (± 4 days)	8 weeks (± 4 days)	Day 1	Week 4 (± 4 days)	Week 8 (± 4 days)		
Pregnancy test (female subjects of childbearing potential)[h]	X	X	X		X	X	X	X	X
Liver function tests (LFTs)[i]	X		X		X		X	X	X
Amylase and lipase	X		X		X		X	X	X
Ophthalmological examination[j]							X	X	
Ivacaftor or placebo dosing	X	X	X		X	X	X		
Concomitant treatments and procedures	----------Continuous from signing of the ICF and Assent (where applicable) through the Safety Follow-up Visit----------								
Adverse events	----------Continuous from signing of the ICF and Assent (where applicable) through the Safety Follow-up Visit----------								

[h] A urine β-hCG test will be performed at all visits in Treatment Periods 1 and 2 and will be performed before the first dose of study drug on Day 1 of Treatment Periods 1 and 2. A urine β-hCG test will be performed at the ETT visit (as applicable). A serum pregnancy test will be performed at the Safety Follow-up Visit.

[i] ALT, AST, GGT, alkaline phosphatase, and bilirubin

[j] OE is required for subjects who were under 18 years of age at the Screening Visit. OE will be performed either at the Week 8 Visit of Treatment Period 2 or at the ETT Visit. This examination is not required if the subject received study drug for a total of less than 4 weeks.

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
cAMP	cyclic adenosine monophosphate
CF	cystic fibrosis
[redacted]	[redacted]
CFTR	Cystic fibrosis transmembrane conductance regulator gene
CFTR	Cystic fibrosis transmembrane conductance regulator protein
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P_{450}
ECFS-CTN	European Cystic Fibrosis Society - Clinical Trial Network
eCRF	electronic case report form
EDC	electronic data capture
ERS	European Respiratory Society
ETT	Early Termination of Treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
[redacted]	[redacted]
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
[redacted]	[redacted]
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLI	Global Lung Function Initiative
GPS	Global Patient Safety
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IRB	institutional review board
IVA	ivacaftor
IXRS	interactive web or voice response system
LCI	lung clearance index
$LCI_{2.5}$	LCI calculated as lung volume turnovers required to reach 2.5% of the starting nitrogen concentration
[redacted]	
LFT	liver function test

Abbreviation	Definition
MBW	multiple breath washout
MCMC	Markov Chain Monte Carlo method
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures
mRNA	messenger ribonucleic acid
N_2	nitrogen
n	number
OE	Ophthalmologic(al) examination
PE	physical examination
P-gp	P-glycoprotein
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
q12h	every 12 hours
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SUSAR	suspected, unexpected, serious adverse reactions
TEAE	treatment-emergent adverse event
TOBI®	Tobramycin Inhalation Solution
ULN	upper limit of normal
Vertex	Vertex Pharmaceuticals Incorporated

5 INTRODUCTION

5.1 CF and Ivacaftor Background

Cystic fibrosis (CF) is a chronically debilitating autosomal recessive disease with high morbidity and premature mortality that affects approximately 70,000 individuals worldwide[1], including approximately 30,000 individuals in the United States[2] and approximately 39,000 in the European Union (EU).[3] The disease affects predominately Whites[4] and is caused by mutations in the CF transmembrane conductance regulator gene (*CFTR*), which results in absent or deficient function of the CFTR protein at the cell surface.[5] CFTR is an epithelial chloride channel responsible for aiding in the regulation of salt and water absorption and secretion in various tissues. The failure to regulate chloride transport in these tissues results in the multisystem pathology associated with CF.[6] In the lungs, obstruction of airways with thick mucus, establishment of a chronic bacterial infection in the airways, and damaging inflammatory responses are all thought to play a role in causing irreversible structural changes in the lungs and respiratory failure. Progressive loss of lung function is the leading cause of mortality.[2,4] Currently, there is no cure for CF, and, despite adjunctive treatments with nutritional supplements, antibiotics and mucolytics,[7] the median predicted age of survival of individuals born today with CF is approximately 40 years of age.[2,8]

More than 2000 mutations in the *CFTR* gene have been identified.[9] CFTR mutations are grouped into 5 classes depending on the mutation type. This study focuses on the Class V (splice) mutation *3849 + 10kb C→T*, which has a prevalence of 0.2% to 2% globally and the Class X missense mutation *D1152H*, which has a prevalence of <0.1% globally. Both mutations have residual CFTR function: *3849 + 10kb C→T* results in a reduced amount of normal CFTR protein at the cell surface (average sweat chloride 66 mEq/L; 34% of patients with pancreatic insufficiency[9]), while *D1152H* results in normal or elevated levels of CFTR protein at the cell surface but with reduced levels of CFTR function (average sweat chloride 45 mEq/L; 23% of patients with pancreatic insufficiency[9]). These mutations are described further below.

Ivacaftor (Kalydeco®), the first CFTR modulator developed by Vertex Pharmaceuticals Incorporated, is an orally-administered CFTR potentiator that increases the channel-open probability of CFTR protein at the cell surface to enhance chloride transport. Globally, ivacaftor is indicated for the treatment of CF in patients as young as 2 years who have the *G551D* and certain other gating (Class III) mutations as well as the *R117H* mutation in the *CFTR* gene, depending on the country.

5.2 Rationale for Study

Class V *CFTR* mutations include splicing abnormalities that markedly decrease the amount of wild-type CFTR protein at the cell surface.[10,11] One of these Class V mutations, *3849 + 10kb C→T*, is characterized by a partially active splice site in intron 19 that leads to the insertion of a new 84 base pair exon that contains an in-frame stop codon between exon 19 and 20.[12] With this mutation, both correctly and aberrantly spliced *CFTR* transcripts are produced, and the amounts of each may vary between patients.[13] CFTR protein translated from any correctly spliced *CFTR* mRNA is thought to be present and functional at the cell membrane. In an in vitro model system, ivacaftor increased wild-type CFTR chloride transport, and therefore may increase the function of CFTR derived from correctly spliced transcripts available at the cell surface.[14] Therefore, this study will evaluate ivacaftor treatment in subjects with the *3849 + 10kb C→T CFTR* mutation.

D1152H is a missense mutation that results in normal or increased levels of CFTR protein at the cell surface but a reduction in CFTR-mediated chloride transport. In vitro, ivacaftor increased chloride transport in cells expressing D1152H-CFTR.[14] Therefore, this study will also evaluate ivacaftor treatment in subjects with the *D1152H* mutation.

Study VX12-770-113 (Study 113) demonstrated improvements with ivacaftor treatment in subjects with clinical residual CFTR function, and subjects who had a *3849 + 10KB C→T* or *D1152H CFTR* mutation were among those included in Study 113.

[redacted]

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the efficacy of ivacaftor treatment in subjects with CF 6 years of age and older who have a *3849 + 10KB C→T* or *D1152H CFTR* mutation.

[redacted]

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Change from baseline in lung clearance index$_{2.5}$ ($LCI_{2.5}$; calculated as lung volume turnovers required to reach 2.5% of the starting nitrogen [N_2] concentration) through 8 weeks of treatment.

[redacted]

8 STUDY POPULATION

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

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

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, assent form.
2. Male or female with confirmed diagnosis of CF.[15] The subject must have **both** of the following:
   - One or more characteristic phenotypic features, such as chronic cough and sputum production, persistent chest radiograph abnormalities, **or** airway obstruction manifested by wheezing and air trapping; **or** a history of CF in a sibling; **or** a positive newborn screening test result;
   - An increased sweat chloride concentration (≥60 mmol/L) by pilocarpine iontophoresis on 2 or more occasions; **or** identification of 2 CF causing mutations; **or** demonstration of abnormal nasal epithelial ion transport.
3. Six years of age and older and ≥25 kg on the date of the ICF.
4. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
5. A *3849 + 10KB C→T* or *D1152H* mutation on at least 1 *CFTR* allele.
6. FEV_1 ≥40% of predicted and ≤105% of predicted at screening, based on the Global Lung Function Initiative (GLI)-2012 multi-ethnic all-age reference equations.[16]

8.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will **not** be eligible:

1. A *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *R117H* mutation
2. 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 to the subject. For example:
   - A history of cirrhosis with portal hypertension.
   - An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (the first dose of study drug).
3. Ongoing or prior participation in an investigational drug study (including studies investigating lumacaftor/ivacaftor or ivacaftor) within 30 days before the Screening Visit.
   - A washout period of 5 terminal half-lives of the previous investigational study drug or 30 days, whichever is longer, must elapse before the Screening Visit. The duration of the elapsed time may be longer if required by local regulations.
   - Subjects who participated in Vertex Study VX14-661-108 may not be enrolled.

- Ongoing participation in a noninterventional study (including observational studies) is permitted.

4. Any of the following abnormal laboratory values at the Screening Visit:
   - Hemoglobin <10 g/dL
   - Alanine aminotransferase (ALT) or AST >5 × upper limit of normal (ULN)
   - Bilirubin >2 × ULN
   - Glomerular filtration rate ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation in subjects <18 years of age and the Modification of Diet in Renal Disease equation in subjects ≥18 years of age).[17,18,19]
5. For subjects <18 years of age at the Screening Visit, evidence of cataract/lens opacity determined to be clinically significant by the ophthalmologist or optometrist during the ophthalmologic examination (OE) at the Screening Visit.
6. Use of any moderate or strong inducers or inhibitors of cytochrome P450 (CYP) 3A, including consumption of certain herbal medications (e.g., St. John's Wort) and certain fruit and fruit juices, within 14 days before Day 1 (the first dose of the study drug).
7. Pregnant, breastfeeding, or planning to become pregnant during the study.
8. Sexually active subjects of reproductive potential must be willing to use appropriate contraception.
9. Subject, or close relative of the subject, is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site.

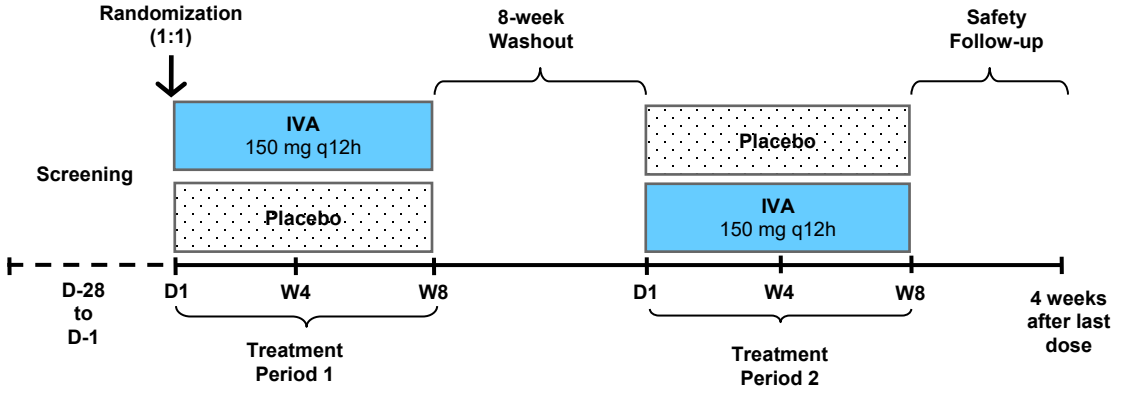
9 STUDY IMPLEMENTATION

9.1 Study Design

This is a randomized, double-blind, placebo-controlled, single-center, crossover study that includes two 8-week treatment periods separated by an 8-week washout period (Figure 9-1). There will be 7 study visits, not including the Screening Visit. The total study duration for each subject will be approximately 32 weeks, including the Screening and the Follow-up periods.

- Sequence 1: ivacaftor (150 mg q12h) in Treatment Period 1; washout; placebo in Treatment Period 2
- Sequence 2: placebo in Treatment Period 1; washout; ivacaftor (150 mg q12h) in Treatment Period 2

Figure 9-1 VX16-770-127 Study Design



9.1.1 Screening

The Screening Visit will occur within 28 days before the first dose of study drug to confirm that the subjects meet the selection criteria for the study. The assessments to be conducted are shown in Table 3-1. The investigator (or appropriate authorized designee) will obtain informed consent and assent, if applicable, from each subject.

If there is documentation of an OE that met protocol criteria and was conducted within 3 months before the Screening Visit, the subject is not required to have another OE during Screening (Section 11.5.5).

9.1.1.1 Repetition of Screening Assessments

Repetition of individual screening assessment(s) that did not meet eligibility criteria is not permitted with the following exceptions:

- If there is clear evidence of a laboratory error (e.g., hemolyzed sample) or equipment malfunction, collection of a repeat sample for the appropriate laboratory test or assessment may be permitted with the approval of the medical monitor
- Exclusionary liver function test (LFT) levels, which may be retested within 14 days of the original screening date
- If screening spirometry measurements fail to meet acceptability and repeatability criteria as specified by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines[20], repeat spirometry evaluation may be performed once.

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 only be rescreened with the approval of the medical monitor. If a subject is rescreened, all screening assessments will be repeated except for follicle-stimulating hormone (FSH) level (if serum FSH level was ≥40 mIU/mL during prior screening), sweat chloride, and OE (if performed within the last 3 months). If a subject is rescreened, the screening window will begin once the first rescreening assessment has been initiated.

9.1.1.3 Extension of the Screening Period Window

A subject may have the Screening Period window extended by 1 week 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
- Additional time to conduct OEs (Section 11.5.5).

9.1.2 Treatment Period

9.1.2.1 Treatment Period 1

Treatment Period 1 will last approximately 8 weeks. Subjects will be randomized to 1 of 2 sequences, as shown in Section 9.1.

Study visits during Treatment Period 1 will occur as shown in Table 3-2. Subjects will be outpatients during Treatment Period 1. All visits should occur within the windows specified.

For subjects who are on a stable regimen of inhaled cycling antibiotics, the Day 1 Visit (beginning of Treatment Period 1) should be timed to occur at the end of an off-cycle but no less than 14 days after the last dose of inhaled antibiotics in the previous on-cycle. The first dose of study drug will be administered on Day 1. The first dose of a new cycle of inhaled cycling antibiotic should also occur on Day 1. Dosing details are given in Section 9.6.

Subjects who prematurely discontinue study drug treatment will be asked to come to the study site for an Early Termination Visit and a Safety Follow-Up Visit, as described in Section 9.1.4.

9.1.2.2 Washout Period

Subjects will have a Washout Period lasting 8 weeks (± 4 days). No visits are scheduled during the Washout Period. If a subject's Washout Period is >8 weeks, the continuation of the subject into Treatment Period 2 will be discussed on a case by case basis with the medical monitor.

9.1.2.3 Treatment Period 2

Treatment Period 2 will last approximately 8 weeks. Study visits during Treatment Period 2 will occur as shown in Table 3-2. Subjects will be outpatients during Treatment Period 2. All visits should occur within the windows specified.

In order to participate in Treatment Period 2, subjects must not have an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before the Treatment Period 2, Day 1 Visit (first dose of study drug in Treatment Period 2) and must not have any significant “non-CF-related” illness within 2 weeks before the Treatment Period 2, Day 1 Visit. “Significant illness” is defined as an acute (serious or nonserious) condition (e.g., gastroenteritis) in the opinion of the investigator. If a subject does not meet these criteria, then the continuation of the subject into Treatment Period 2 will be discussed with the medical monitor (postponed to achieve 28 days from the illness).

For subjects who are on a stable regimen of inhaled cycling antibiotics, the Treatment Period 2, Day 1 Visit should occur at the end of an off-cycle but no less than 14 days after the last dose of inhaled antibiotics in the previous on-cycle. The first dose of study drug in Treatment Period 2 will be administered at the Day 1 Visit. The first dose of a new cycle of inhaled cycling antibiotic should also occur on the Day 1 Visit. Dosing details are provided in Section 9.6.

9.1.3 Follow-up

Subjects will have a Safety Follow-up Visit approximately 4 weeks after the last study drug dose to assess for safety and other outcomes. Safety Follow-up Visit assessments are listed in Table 3-2.

9.1.4 Early Termination of Treatment

Subjects who prematurely discontinue study drug treatment will be asked to come to the study site for an Early Termination of Treatment (ETT) Visit as soon as possible after stopping study drug, and the Safety Follow-up Visit approximately 4 weeks after the last dose of study drug, to assess for safety and other outcomes. If the ETT Visit occurs ≥3 weeks after the last dose of study drug, the Follow-up Visit will not be required. The ETT Visit assessments are listed in Table 3-2.

9.2 Method of Assigning Subjects to Treatment Groups

An interactive web or voice response system (IXRS) will be used to randomize subjects who meet the eligibility criteria to 1 of 2 treatment sequences. Subjects will be randomized in a 1:1 ratio, stratifying for age (6 to 11 years, and ≥12 years) and FEV_1 severity (<60%, and ≥60%).

9.3 Rationale for Study Design and Study Drug Regimens

9.3.1 Study Design

A crossover design with a 1:1 randomization to the 2 treatment sequences will enable within-subject comparison of the effects of ivacaftor for many endpoints, including lung clearance index (LCI). In addition to the increased power of a crossover study design in this study with a limited population of potential subjects, the design provides periods of both active and placebo treatment to allow evaluation of the efficacy and safety of ivacaftor. Given the intent to evaluate efficacy with respect to LCI, the use of placebo is necessary in order to provide a robust assessment. No subject will be disadvantaged by the use of placebo, as no active therapy is withdrawn, and all will have the potential to benefit during the ivacaftor treatment period due to the crossover nature of the study design.

The 8-week crossover period with an 8-week washout period was chosen to accommodate cycling inhaled antibiotic needs in this subject population; additionally, this design successfully yielded strong efficacy and safety results in Study VX12-770-111 where the impact of ivacaftor was evaluated in subjects with CF aged 6 years and older with a *CFTR* gating mutation.

An 8-week period was selected as the duration for the Washout Period because, based on previous studies, no residual effects of ivacaftor are expected by the end of the 8-week washout period. It is expected that some subjects will be on 28-day-on/28-day-off cycles of stable CF medication, as discussed in Section 9.5.1. An 8-week washout period is compatible with these cycles.

9.3.2 Study Drug Dose and Duration

An ivacaftor regimen of 150 mg every 12 hours (q12h) was selected because it is the approved regimen for the treatment of CF in patients with who are 6 years of age and older weighing ≥25 kg.

The 8-week duration of dosing in each Treatment Period was chosen based on results of the ivacaftor program. Clinical studies have shown a clear improvement of $ppFEV_1$ after 8 weeks of treatment.

9.3.3 Study Assessments

[redacted]

Multiple breath washout (MBW) for LCI values: LCI is a measure of ventilation inhomogeneity that is based on tidal breathing techniques that has been evaluated in patients as young as infants.[21,22] Studies have shown that LCI correlates with FEV_1 in its ability to measure airway disease in patients with impacted spirometry assessment but can also detect lung disease at an earlier stage than spirometry.[23,24] Furthermore, data from Study VX10-770-106 (Study 106) in CF subjects aged 6 years and older with an FEV_1 >90% predicted showed LCI to be a more sensitive outcome measure than FEV_1. Given the potential advantages of a more sensitive measurement of lung function than spirometry, LCI will be used as the primary endpoint in this study. $LCI_{2.5}$ (see Section 11.4.1) will be used for the primary endpoint as it represents an optimal balance between time to perform the assessment and sensitivity.[25] [redacted]

[redacted]

9.4 Study Restrictions

Certain medications are not allowed from 14 days before the first dose of study drug through the end of the treatment period (Table 9-1). A nonexhaustive list of prohibitions and cautions for food and medication will be provided in the Study Reference Manual.

Table 9-1 Prohibited Medications

	Study Period	
Medication	**Screening Period**	**Treatment Period 1 Through Treatment Period 2 or ETT (if applicable)**
Strong and moderate CYP3A inducers	None allowed within 14 days before the first dose of study drug	None allowed
Strong and moderate CYP3A inhibitors	None allowed within 14 days before the first dose of study drug	None allowed

Note: The use of restricted medication in subjects with a medical need will be addressed on a case-by-case basis with the medical monitor.

Clinical studies showed that ivacaftor has the potential to inhibit CYP3A and P-glycoprotein (P-gp) substrates. In vitro studies suggest that ivacaftor may inhibit CYP2C9 substrates. Each investigator should evaluate the benefit-risk ratio of using such drugs concomitantly with ivacaftor during this study and should discuss any concerns regarding the use of these substrates with the medical monitor.

9.5 Prior and Concomitant Medications

Information regarding all prior and concomitant medications, including the subject's CF medications, other medications, and herbal and naturopathic remedies administered from 30 days before the Screening Period through the Safety Follow-up Visit will be recorded in each subject's source documents and electronic case report form (eCRF). For subjects who are screened but are not enrolled in the study, details of prior medications will only be documented in the subjects' source documents.

Information about bronchodilator use during the study will be collected and documented in the subject's source documents and eCRF.

9.5.1 Maintenance of Stable Medication Regimen for CF

It is recommended that subjects remain on stable CF medication regimens from 4 weeks before Day 1 through the end of the study. A stable medication regimen is defined as a medication regimen that the subject has been following for at least 4 weeks before Day 1.

Specific requirements apply to certain CF medications:

- At the time of study entry, subjects who are on a stable regimen of a single inhaled antibiotic that is continuously administered should remain on this antibiotic through the Safety Follow-up Visit.
- At the time of study entry, subjects who are on a stable regimen of a single inhaled cycling antibiotic (e.g., Tobramycin Inhalation Solution [TOBI®] regimen), should remain on this antibiotic through the Safety Follow-up Visit. Inhaled cycling antibiotics should be administered in 28-day-on/28-day-off cycles. Study visits on Day 1 and Week 8 during Treatment Periods 1 and 2 should be timed to occur at the end of an off-cycle, but no fewer than 14 days after the last dose of inhaled antibiotics in the previous on-cycle.
- At the time of study entry, subjects who are on an alternating regimen of inhaled cycling antibiotics that comprise continuous administration of antibiotics (e.g., TOBI administration

alternating with Cayston®) should remain on these antibiotics according to their alternating regimens through the Safety Follow-up Visit.

9.6 Administration

Study drug tablets will be administered orally. During Treatment Period 1 and Treatment Period 2 subjects will take 1 tablet (ivacaftor [150 mg] or matching placebo) twice per day.

Study drug should be administered within 30 minutes of consuming fat-containing food such as a standard CF high-fat, high-calorie meal or snack according to the following guidelines:

- All doses of study drug (morning and evening, as applicable) should be administered at approximately q12 h (± 2 hours) on each dosing occasion (e.g., if the morning doses of study drug are administered at 08:00 hours on Day 1, all subsequent morning doses should be administered between 06:00 hours and 10:00 hours).
- At study visits during the treatment periods, the morning dose of study drug will be administered at the site after predose assessments have been completed. The meal or snack will be provided by the site for the morning dose of study drug.
- If a subject's scheduled visit is to occur in the afternoon, the following guidelines must be used for administering either the morning or evening dose:
    - If the dose in the clinic will be within 6 hours of the subject's scheduled morning dose, the subject should withhold their morning dose of study drug and the morning dose will be administered in the clinic.
    - If the dose in the clinic will be more than 6 hours after the subject's scheduled morning dose, the subject should take the morning dose at home and the evening dose will be administered in the clinic. In this event, all assessments will be collected relative to the evening dose.
- For the visit at the end of each treatment period, subjects will be instructed to bring all used and unused study drug to the site; study drug will be dispensed at each visit, as appropriate.

9.7 Dose Modification for Toxicity

If any unacceptable toxicity arises, individual subjects will discontinue dosing (Section 9.8).

9.8 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. Study drug treatment will be withdrawn for any female subject who has a confirmed pregnancy and for any male subject whose female partner has a confirmed pregnancy. A subject may be withdrawn from study drug treatment after a discussion between the investigator and the medical monitor for any of the following reasons:

- The subject develops a medical condition that requires prolonged concomitant therapy with a prohibited medication or prolonged interruption of the study drug.
- The subject has an increase in transaminases for which withdrawal of study drug is recommended, as described in Section 11.5.3.

- The subject develops a cataract.

If a subject has been withdrawn from study drug treatment, the subject will continue to be followed, provided the subject has not withdrawn consent.

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

If the subject withdraws consent for the study, no further evaluations will be performed and no additional data will be collected. Vertex may retain and continue to use any data collected before such withdrawal of consent.

9.9 Replacement of Subjects

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

10 STUDY DRUG INFORMATION AND MANAGEMENT

10.1 Preparation and Dispensing

Study drug may be dispensed only under the supervision of the investigator or an authorized designee to the subject or the subject's legally appointed and authorized representative (e.g., parent or legal guardian) for administration to the subject.

10.2 Packaging and Labeling

Vertex will supply Ivacaftor and placebo tablets in child-resistant weekly blister cards. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing will be included 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 as detailed in Section 10.5. 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	Formulation/ Route	Packaging (Formulation Strength)	Storage Condition
Ivacaftor	Oral	Supplied as 150-mg tablets	25ºC (77ºF) with excursions to 30ºC (86ºF)

10.4 Study Drug Interruption

If study drug dosing must be interrupted for more than 72 hours, the medical monitor must be notified. In these instances, study drug dosing may resume only after approval by the medical monitor. Specific instructions for interruption for elevated LFT levels are provided in Section 11.5.3.

10.5 Drug Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of study drug received, study drug dispensed to the subjects, and 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 at each visit. These materials will be retained at the site according to instructions provided by Vertex or its designee until inventoried by the study monitor. The study monitor will review study drug records and inventory throughout the study.

10.6 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. At the end of the study, the study monitor will provide instructions as to the disposition of any unused investigational product. If the study monitor authorizes destruction at the study site, the investigator will ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Vertex. Destruction will be adequately documented.

10.7 Compliance

Study drug doses administered during inpatient periods will be administered under the direct supervision of the investigator or designee in the clinical research unit to ensure 100% study treatment compliance.

For study drug doses administered during the outpatient periods of the study, drug accountability will be assessed at each visit by counting returned dosage units. Discrepancies will be discussed with the subject and recorded in the source documents. If subjects demonstrate continued noncompliance of study drug dosing despite educational efforts, the investigator will contact the medical monitor to discuss discontinuing the subject from the study.

10.8 Blinding and Unblinding

This will be a double-blind study.

10.8.1 Blinding

Subjects and all site personnel, including the investigator, site monitor, and study team, will remain blinded to treatment assignments until database lock. The Vertex study team will remain blinded to treatment assignments until all subjects have completed the study. Exceptions are made for the following personnel:

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

- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy serious adverse event (SAE) processing and reporting regulations
- Unblinded statistician who will prepare the final (production) randomization list (this statistician is not part of the study team)
- Vertex IXRS Management for IXRS oversight and system administration
- Vertex Clinical Supply Chain
- The bioanalytical laboratory/vendor personnel managed by Vertex Bioanalysis

Vertex Quality Assurance GCP personnel and all other Vertex Bioanalysis laboratory personnel will be blinded to the treatment assignment.

10.8.2 Unblinding

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

Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators will use their best judgment as to whether to unblind without first attempting to contact the medical monitor to discuss and agree to the need for unblinding. If investigators deem it not necessary to unblind immediately, they will first attempt to contact the medical monitor to discuss and agree to the need for unblinding. If investigators have tried but are unable to reach the medical monitor, they will use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the medical monitor.

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

In addition, the Vertex Medical Information Call Center ([redacted]) will answer calls 24 hours a day, 7 days a week, 365 days of the year, and will triage these calls to the study medical monitor or appropriate backup.

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

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

11 ASSESSMENTS

11.1 Timing of Assessments

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

[redacted]

Vital sign assessments will be performed before blood draws.

Liver function testing and urine pregnancy testing may be completed predose or postdose.

11.2 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history (includes recording CF genotype), height, and weight.

[redacted]

11.4 Efficacy

11.4.1 MBW

LCI is derived from N_2 MBW testing and will be conducted at visits specified in Table 3-1 and Table 3-2 to evaluate the effect of ivacaftor on lung ventilation inhomogeneity. $LCI_{2.5}$ represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value, [redacted].[25]

Each MBW will be performed in multiple replicates for each visit, and the mean LCI value at each visit will be calculated by the sponsor or sponsor designee using all technically acceptable washout replicates provided by the central reader.

During the Screening Period, the MBW test may be performed pre‑ or post‑bronchodilator. At all other visits, all MBW tests should be performed "pre‑bronchodilator" [redacted]. MBW testing must be performed before dosing, unless noted otherwise.

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

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

In the event that a subject forgets to withhold bronchodilator(s), MBW testing should be performed according to the following:

- If the subject's Day 1 (in each treatment period) MBW test is pre-bronchodilator, but on a subsequent visit, the subject forgets to withhold bronchodilator use, post-bronchodilator MBW testing will be obtained for that visit only, and the visit will not be rescheduled.
- If at the subject's Day 1 (in each treatment period) MBW test, the subject forgets to withhold his/her dose of bronchodilator, MBW testing should be performed post-bronchodilator and all subsequent MBW testing should be performed post-bronchodilator.
- Each MBW test will be recorded in the source documents as pre-bronchodilator or post-bronchodilator.

Detailed LCI procedures will be supplied in the Study Reference Manual.

Subjects and their parent/caregiver should not be informed of their study-related LCI results during the study regardless if the subject has prematurely discontinued treatment.

[redacted]

11.5 Safety

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

11.5.1 Adverse Events

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

11.5.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory with the exception of urine pregnancy tests, which will be analyzed locally. On Day 1, blood samples will be collected before the first dose of the study drug. At all other scheduled visits, these samples will be collected at any time during the visit.

Blood and urine samples for clinical laboratory assessments will be collected as shown in Table 3-1 and Table 3-2). 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 at Screening	Hematology at Screening	Liver Function Tests[a]
Glucose	Hemoglobin	Bilirubin, direct bilirubin
Blood urea nitrogen	Erythrocytes:	Aspartate aminotransferase
Creatinine	Mean corpuscular hemoglobin	Alanine aminotransferase
Sodium	Mean corpuscular hemoglobin concentration	Gamma glutamyl transferase
Potassium	Mean corpuscular volume	Alkaline phosphatase
Calcium	Platelets	
Chloride	Reticulocytes (absolute)	
Magnesium	Leukocytes	
Bicarbonate	Differential (absolute and percent):	
Phosphate	Eosinophils	
Bilirubin, direct bilirubin	Basophils	
Alkaline phosphatase	Neutrophils	
Aspartate aminotransferase	Lymphocytes	
Alanine aminotransferase	Monocytes	
Amylase[a]		
Lactate dehydrogenase		
Lipase[a]		
Gamma glutamyl transferase		
Protein		
Albumin		
Creatine kinase		

[a] Amylase, lipase, and LFTs performed at screening and at other Visits as indicated in Table 3-2.

Pregnancy Testing for Female Subjects of Childbearing Potential

Serum samples will be analyzed at the central laboratory. Urine beta-human chorionic gonadotropin (β-hCG) tests will be performed at the study site. The urine pregnancy test at Day 1 of each treatment period must be negative before the first dose of study drug.

If a urine pregnancy test is positive, all study drug dosing will stop and the pregnancy will be confirmed with a serum (β-hCG) test. If the subject is pregnant, the procedures outlined in Section 11.5.6.2 will be followed.

Additional Evaluations

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

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

11.5.3 Elevation of Liver Function Test Parameters

Elevation of LFT Parameters

Subjects with new treatment-emergent ALT or AST elevations of >3 × ULN must be followed closely, including repeat confirmatory testing performed by the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT and AST levels, as clinically indicated. In addition, if ALT or AST are >5 × ULN, repeat follow-up levels must be obtained within 7 ± 2 days and followed up 7 days later. If a subject cannot return to the site for liver function testing, a local laboratory may be used. Elevations in LFTs at the local laboratory 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).

LFT Elevations Leading to Study Drug Interruption

Study drug administration must be interrupted immediately and the medical monitor must be notified if any of the following criteria is met:

- ALT or AST >5 × ULN, or
- ALT or AST >3 × ULN in association with elevation of bilirubin >2 × ULN and/or clinical jaundice

Repeat testing should be performed within 48 to 72 hours to confirm the initial elevation. A thorough investigation of potential causes should be conducted and the subject should be followed closely for clinical progression. If no convincing alternative etiology for the elevated transaminases is identified, regardless of whether ALT or AST levels have improved, the subject must be discontinued from the study in consultation with the medical monitor (Section 9.8). Subjects in whom treatment is discontinued for elevated transaminases should have their transaminases monitored closely until levels normalize or return to baseline. If an alternative cause of transaminase elevation has been identified, study drug may be resumed once transaminases return to ≤2 × ULN. Approval of the medical monitor is required before resumption of study drug. Upon resumption of study drug, transaminases should be assessed weekly for 4 weeks. If a protocol-defined transaminase elevation occurs 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.

11.5.4 Physical Examinations and Vital Signs

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

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

Vital signs include blood pressure (systolic and diastolic), body temperature, pulse rate, and respiration rate. These will be assessed following at least a 5-minute rest in the supine position.

11.5.5 Ophthalmologic Examination

Subjects who are under 18 years of age at the Screening Visit will undergo an OE at the time points in Table 3-1 and Table 3-2. The OE will include:

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

These examinations must be conducted by a licensed ophthalmologist or optometrist. If there is documentation of an OE that met protocol criteria and was conducted within 3 months before the Screening Visit, the subject is not required to have another OE during Screening.

If a cataract or lens opacity is identified and determined to be clinically significant by the ophthalmologist or optometrist, the subject (and the subject's parent or guardian if the subject is a minor) will be notified.

Additional OEs may be conducted at the discretion of the investigator. The Vertex medical monitor or designee should be notified of any additional OEs.

In addition, at Screening, the following history will be obtained for all subjects:

- history of steroid use
- history of trauma to the eye
- any family history of glaucoma, congenital cataracts, or cataracts arising later in life

11.5.6 Contraception and Pregnancy

11.5.6.1 Contraception

Ivacaftor did not show any genotoxic potential in a standard battery of in vitro and in vivo studies. Ivacaftor also did not show any teratogenic potential in developmental and reproductive toxicology studies.

Ivacaftor has been studied with an estrogen/progesterone oral contraceptive and was found to have no significant effect on the exposures of the oral contraceptive. Ivacaftor is not expected to modify the efficacy of oral contraceptives. Therefore, hormonal contraceptives will be acceptable as a means of contraception for female subjects of childbearing potential in this study.

Definition of Childbearing Potential

All female subjects who have had their first menstrual period, from the time of the Screening Visit through the Follow-up Visit, including subjects with tubal ligations, will be considered to be of childbearing potential unless:

- The subject has had a documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy.
- The subject is postmenopausal, defined as at least 12 months of continuous spontaneous amenorrhea with serum FSH levels ≥40 mIU/L.

11.5.6.2 Pregnancy and Nursing Mothers

Subjects will be counseled to inform the investigator if they (or their female partner) are pregnant or plan to become pregnant or are breastfeeding or planning to breastfeed during study treatment and for 90 days after the last dose of study drug. An exception is made for pregnancies in the female partners of male subjects when the pregnancy resulted from donated sperm or sperm banked before study drug exposure.

If a female subject or a male subject's female partner becomes pregnant, the pregnancy must be reported to Vertex Global Patient Safety within 24 hours of the site's knowledge of the pregnancy while confirmation is pending. Once the pregnancy is confirmed with a serum pregnancy test, study drug will be permanently discontinued. Pregnancy does not constitute an AE.

Once a pregnancy is confirmed, pregnant female subjects or female partners of male subjects will be followed until delivery or the end of pregnancy (i.e., delivery, stillbirth, miscarriage), 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.

12 STATISTICAL AND ANALYTICAL PLANS

Analyses of efficacy and safety data will be described in a statistical analysis plan (SAP). The SAP will be finalized before database lock for the final analysis.

12.1 Sample Size and Power

No formal sample size calculation was conducted. The planned sample size of approximately 50 subjects is based on the number of subjects expected to be available for participation.

Assuming an estimated standard deviation (SD) of the paired differences of 1.00 in $LCI_{2.5}$, this available sample size of 50 subjects will produce a 2-sided 95% confidence interval (CI) of the mean treatment difference with precision (margin of error) of 0.28 points. Similarly, the margin of error using a 2-sided 80% CI will be 0.18 points.

12.2 Analysis Sets

The Full Analysis Set (FAS) is defined as all randomized subjects who have received at least 1 dose of study drug.

The Safety Set is defined as all enrolled subjects who received at least 1 dose of study drug. The Safety Set is to be used for all safety analyses in which subjects will be analyzed according to the treatment they received and not according to their randomized treatment group.

12.3 Statistical Analysis

This section summarizes the planned statistical analyses of efficacy and safety. The Vertex Biometrics department or a designated CRO will conduct these analyses. SAS® Version 9.2 or higher will be used to generate all statistical outputs (tables, figures, listings, and data sets).

12.3.1 General Considerations

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

Categorical variables will be summarized using counts and percentages.

Unless specified otherwise, only descriptive analyses will be performed (i.e., no statistical hypothesis testing will be performed).

Baseline: Study baseline is defined as the most recent nonmissing measurement collected before the first administration of study drug in Treatment Period 1. Period baseline is defined as the most recent nonmissing measurement collected before the first administration of study drug in each Treatment Period. For Treatment Period 1, the period baseline will be the study baseline; for Treatment Period 2, the period baseline will be from an assessment measured after the Washout Period and before the first administration of study drug in Period 2.

For all efficacy analyses, the statistical inference will be based on change from study baseline. However, efficacy analyses based on change from period baseline will also be presented. Similarly, summary tables, as applicable, will be presented based on both baselines.

All subject data, including those derived, will be presented in the subject data listings; listings will display all subjects who were randomized, regardless of whether or not they received study drug.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

The number and percentage of subjects in each disposition category (e.g., randomized, included in the FAS, included in the Safety Set, completing treatment period, and discontinuing study, with reasons for discontinuation) will be summarized by treatment sequence and overall.

12.3.2.2 Demographics and Baseline Characteristics

The demographics and baseline characteristics summary will be presented by treatment sequence for FAS. Background (e.g., medical history) summary will be presented by treatment sequence for the FAS.

12.3.2.3 Prior and Concomitant Medications

Medications taken 30 days before the Screening Visit and up to the Safety Follow-up Visit will be summarized by preferred term using the World Health Organization-Drug Dictionary Enhanced for the FAS as frequency tables in 2 parts:

- Prior medication: medication that started before the first dose of study drug, regardless of when dosing of the medication ended.
- Concomitant medication: medication received at or after the first dose of study drug, medication that was received before initial dosing and continued after initial dosing of study drug, or medication with missing stop date.

Medication that started before the first dose of study drug and continued after the first dose of study drug will be summarized as prior medication and separately as concomitant medication. Medications with a missing start date will be considered to have a start date before the first dose of study drug.

Prior medications will be summarized by treatment sequence, and concomitant medications will be summarized by treatment group.

12.3.2.4 Study Drug Exposure and Compliance

Exposure to study drug and dosing compliance will be summarized for the FAS by means of summary statistics.

Dosing compliance will be summarized for each treatment period for the FAS, and is calculated as the actual number of dosing occasions at which study drug was administered, as a percentage of the planned number of dosing occasions.

12.3.3 Efficacy Analysis

Efficacy analyses will be based on the FAS unless noted otherwise, and the statistical inference will be based on change from study baseline. All efficacy data will be presented in subject data listings.

12.3.3.1 Change from Baseline in LCI

A Bayesian approach will be used to estimate the effect of ivacaftor versus placebo on change from study baseline in $LCI_{2.5}$. A non-informative prior distribution (normal distribution with mean 0 and variance = 10^6) on the treatment difference will be assumed. The posterior distribution of the treatment difference will be obtained using the Markov Chain Monte Carlo (MCMC) method. The mean of the posterior distribution will be calculated and the 80% credible interval for the treatment difference will be provided. Using this Bayesian method, the posterior probability that the treatment difference for $LCI_{2.5}$ is less than zero will be calculated. The study will be considered successful if this probability exceeds 80%.

Supportive analyses of absolute change from study baseline in $LCI_{2.5}$ through Week 8 of each double-blind treatment period based on a mixed-effects model for repeated measures (MMRM) using the FAS will be performed.

The model will include the absolute change from the study baseline in each treatment period as the dependent variable; sequence, treatment, treatment period, and visit within treatment period as fixed effects; $LCI_{2.5}$ at study baseline as covariate if deemed necessary; and subject nested within sequence as the random effect. An unstructured covariance matrix will be used for the repeated measurements of the same subject within each treatment period. If there is a convergence problem for the unstructured covariance matrix, an appropriate covariance matrix structure, such as compound symmetry, will be assumed in the primary analysis. The estimated mean treatment difference overall, and a 80% confidence interval will be provided.

Carry-over effect will be assessed by the sequence effect in the model, as well as by comparing baseline for each treatment period. If there is a clinically or statistically significant unequal carry-over effect, then the data from the first period may be used for the analysis.

[redacted]

12.3.5 Safety Analysis

The overall safety profile of ivacaftor will be assessed in terms of:

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (e.g., LFTs)
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) and PEs
- OEs (for subjects less than 18 years of age)

Safety analyses will be based on the Safety Set. All safety data will be presented in subject data listings.

12.3.5.1 Adverse Events

AEs will be coded according to MedDRA. The number and percentage of subjects experiencing an AE will be summarized by the MedDRA system organ class and preferred term. AEs will be classified as pre-treatment or treatment-emergent.

Pre-treatment AEs are defined as AEs that were reported or worsened after signing the ICF up to the start of study drug dosing.

Treatment-emergent AEs are defined as AEs that were reported or worsened on or after the start of study drug dosing through the Safety Follow-up Visit.

Only TEAEs will be summarized in tables. Some rules that will apply to the summarization of AEs are (1) a subject with multiple occurrences of the same AE or a continuing AE will only be counted once; (2) only the maximum severity level will be presented in the severity summary; and (3) only the worst relationship level will be presented in the relationship summary.

AEs leading to death, SAEs, dose interruption, and permanent discontinuation will be listed separately. All AEs through the Safety Follow-up Visit, including pre-treatment AEs, will be listed in a subject data listing.

12.3.5.2 Clinical Laboratory Assessments

All statistical summaries of laboratory values will be performed using SI units. LFT results will be summarized by treatment group at each scheduled time point. Changes from baseline will also be summarized. Maximum shift changes from baseline based on the LFT normal ranges will be tabulated by treatment. A subject data listing of abnormal LFT values from scheduled and unscheduled time points will be provided. Results for hematology and for chemistry assessments other than LFTs will be listed. Clinically significant abnormal laboratory findings will be reported as AEs.

12.3.5.3 Vital Signs

Systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), respiratory rate (breaths per minute), and body temperature (degrees C) will be summarized by treatment. Changes from baseline will also be summarized. Clinically significant abnormal findings will be reported as AEs.

12.3.5.4 Physical Examination

PE results performed as part of the Screening Period assessment will be presented in subject data listings only. Clinically relevant results identified after screening will be reported as AEs.

12.3.5.5 Ophthalmological Examinations

Ophthalmological examination will be done for subjects who are under 18 years of age at the Screening Visit and then either at the Week 24 Visit or at the ETT Visit. This examination is not required if the subject received study drug for a total of less than 4 weeks.

Ophthalmologic examination findings will be presented as a data listing. Summary tables will be provided if deemed necessary and as appropriate.

12.3.6 Interim and IDMC Analyses

12.3.6.1 Interim Analysis

No interim analysis is planned.

12.3.6.2 IDMC Analysis

Not applicable.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

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

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

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

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

13.1.1.3 Documentation of Adverse Events

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

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, the **earliest** of:
  - 28 days after the last dose of study drug, or
  - The Early Treatment Termination Visit, if that visit is 3 weeks or later after the last dose of study drug (see Section 9.1.4).

All subjects will be queried, using nonleading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms will be identified as 1 overall event or diagnosis. All AEs for enrolled subjects will be recorded in the eCRF and source document. AEs for subjects who are screened but not subsequently enrolled in the study 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 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed August 2015). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." In 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 given in the CTCAE. The severity of an AE that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

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

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 presented 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 study subject's medical record).

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 shown in Table 13-3.

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

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

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 shown 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)

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, hospitalization, 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 in the study 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 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. 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**.

SAEs will be recorded on the Vertex Organized 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 to Vertex the outcome of the event using the SAE Form.

13.1.2.3 Reporting Serious Adverse Events

The investigator is responsible for notifying the sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. 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]

Contact Telephone: [redacted]

13.1.2.4 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 and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to central independent ethics committees (IECs).

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

13.2 Administrative Requirements

13.2.1 Ethical Considerations

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

13.2.2 Subject Information and Informed Consent

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

13.2.3 Investigator Compliance

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

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

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

13.2.6 Record Retention

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

13.2.7 Study Termination

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

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

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

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

13.3 Data Quality Assurance

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

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each enrolled subject will be entered into an eCRF 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 eCRF and documented in an audit trail, which will be maintained within the clinical database.

13.4 Monitoring

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

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

13.5 Electronic Data Capture

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

An eCRF 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 eCRF. Source documentation supporting the eCRF 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 eCRF 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 eCRFs, including any changes made to the eCRFs, to endorse the final submitted data for the subjects for whom the investigator is responsible.

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

13.6 Publications and Clinical Study Report

13.6.2 Clinical Study Report

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

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX16-770-127	Version #: 1.0	Version Date: 20 October 2016
Study Title:A Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy of Ivacaftor in Subjects with Cystic Fibrosis Who are 6 Years of Age and Older and Have Either a 3849 + 10KB C→T or D1152H-CFTR Mutation		

This Clinical Study Protocol has been reviewed and approved by the sponsor.

Printed Name	Title
Signature	Date

15.2 Investigator Signature Page

Protocol #: VX16-770-127	Version #: 1.0	Version Date: 20 October 2016
Study Title:A Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy of Ivacaftor in Subjects with Cystic Fibrosis Who are 6 Years of Age and Older and Have Either a 3849 + 10KB C→T or D1152H-CFTR Mutation		

I have read Protocol VX16-770-127, Version 1.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-770 and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date