1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3b, 2-part, Randomized, Double-blind, Placebo-controlled Crossover Study With a Long-term Open-label Period to Investigate Ivacaftor in Subjects With Cystic Fibrosis Aged 3 Through 5 Years Who Have a Specified *CFTR* Gating Mutation

Vertex Study Number: VX15-770-123

[redacted]

EudraCT Number: 2015-001267-39

Date of Protocol: 12 April 2017 (Version 4.0)

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

2 PROTOCOL SYNOPSIS

Title A Phase 3b, 2-part, Randomized, Double-blind, Placebo-controlled Crossover Study With a Long-term Open-label Period to Investigate Ivacaftor in Subjects With Cystic Fibrosis Aged 3 Through 5 Years Who Have a Specified *CFTR* Gating Mutation

Brief Title A Study to Evaluate Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis Aged 3 Through 5 Years Who Have a Specified *CFTR* Gating Mutation

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

Objectives

Primary Objective

To evaluate the efficacy of ivacaftor treatment, as measured by lung clearance index (LCI), in subjects with cystic fibrosis (CF) who have a specified CF transmembrane conductance regulator (*CFTR*) gating mutation and are 3 through 5 years of age at the start of the study.

Secondary Objectives

To evaluate the following in subjects with CF who have a specified *CFTR* gating mutation and are 3 through 5 years of age at the start of the study:

[redacted]

- Disease progression as measured by changes in pancreatic function
- The safety of ivacaftor treatment

Endpoints

Part 1 Endpoints

Primary Endpoint

Absolute change from baseline in $LCI_{2.5}$ through 8 weeks of treatment

Secondary Endpoints

- Absolute change from baseline in serum levels of immunoreactive trypsinogen at 8 weeks of treatment
- Absolute change from baseline in fecal elastase-1 at 8 weeks of treatment
- Absolute change from baseline in weight at 8 weeks of treatment
- Absolute change from baseline in body mass index (BMI) at 8 weeks of treatment
- Safety, as determined by AEs, clinical laboratory values (including LFTs), ophthalmologic examinations (OEs), physical examinations, and vital signs

[redacted]

Part 2 Endpoints

[redacted]

Number of Subjects Approximately 50 subjects will be enrolled.

Study Population Male and female subjects with CF, aged 3 through 5 years, who have 1 of the following specified *CFTR* gating mutations on at least 1 allele: *G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P,* or *G1349D*

Investigational Drug Active substance: ivacaftor

Activity: CF transmembrane conductance regulator protein (CFTR) potentiator

Strength and route of administration: 50-mg and 75-mg granules in capsules or sachets, oral; and 150-mg tablets, oral

Study Duration Excluding the Screening Period, each subject will participate in the study for 148 weeks (± 7 days) (from Day 1 to last day of Follow-up Telephone Contact, Week 148 [± 7 days]).

Following review of study enrollment and assessment of the available number of potential subjects for this study, Vertex decided to close enrollment as of 21 February 2017 and withdraw subjects in order to terminate the study. After the protocol amendment has been approved at a site, subjects in Part 1 will be withdrawn from the study at their Week 24 Visit, and subjects in Part 2 will be withdrawn from the study and requested to complete the Early Termination of Treatment Visit.

Study Design

This is a 2-part, randomized, double-blind, placebo-controlled, crossover study with a long-term open-label period.

In addition to the Screening Period (up to 4 weeks in duration), subject participation is anticipated to last approximately 148 weeks (2 Treatment Periods of 8 weeks each, Washout Period of 8 weeks, Open-label Period of 120 weeks, and Follow-up Telephone Contact approximately 4 weeks after last dose of study drug).

Subjects will be randomized 1:1 to receive 1 of 2 treatment sequences during Part 1:

- Sequence 1: ivacaftor in Treatment Period 1→washout→placebo in Treatment Period 2
- Sequence 2: placebo in Treatment Period 1→washout→ ivacaftor in Treatment Period 2

This study includes:

- Screening Period: Day -28 through Day -1 relative to the first dose of study drug
- Part 1 Treatment Period 1 through Treatment Period 2
  - Treatment Period 1: Day 1 (first dose of study drug) through Week 8
  - 8-week Washout Period
  - Treatment Period 2: Week 16 through Week 24
- Part 2 Open-label Period: Week 24 through Week 144 (the first dose of ivacaftor during the Open-label Period will be given after completion of assessments at the Week 24 Visit); the Week 24 Visit (Part 1) is also considered the first visit of the Open-label Period.
- Follow-up Telephone Contact (4 weeks [±7 days] after the last dose of study drug)

Subjects who prematurely discontinue study drug treatment will be required to complete the Early Termination of Treatment Visit, which is to be scheduled as soon as possible after it is decided that the subject will terminate study drug treatment. Subjects who prematurely discontinue study drug treatment will also be required to complete the Safety Follow-up Visit, approximately 4 weeks (±7 days) after their last dose of study drug. If the Early Termination of Treatment Visit occurs 3 weeks or later following the last dose of study drug, then the Early Termination of Treatment Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

Subjects will continue to complete all other scheduled study visits for assessments of efficacy and other endpoints as detailed in the Schedule of Assessments.

Subjects who discontinue study drug treatment during Part 1 will not be allowed to participate in Part 2 of the study.

Assessments

Efficacy

LCI, [redacted], immunoreactive trypsinogen, fecal elastase-1, [redacted] weight, BMI, [redacted]

Safety

AEs, clinical laboratory values (including LFTs), OEs, physical examinations, and vital signs

Statistical Analyses

Statistical analysis details will be provided in the Statistical Analysis Plan, which will be finalized before the planned interim analysis for Part 1 of the study. For Part 1 (i.e., the Placebo-controlled Crossover Period), 2 types of baseline will be defined:

- Study baseline is defined as the most recent nonmissing measurement collected

prior to the initial administration of study drug in Treatment Period 1.

- Period baseline is defined as the most recent nonmissing measurement collected before the initial administration of study drug in each Treatment Period.

In Part 1, the primary efficacy variable is the absolute change from baseline through 8 weeks of treatment in LCI endpoint. The analysis will be based on a mixed-effects model for repeated measures utilizing the Full Analysis Set. The model will include the absolute change from study baseline in each period as the dependent variable; sequence, treatment, period, and visit within period as fixed effects; LCI baseline and age as covariates; and subject nested within sequence as the random effect. Unstructured covariance matrix is further assumed for the repeated measurements of the same subject within each period.

Efficacy analyses will be based on change from study baseline; however, efficacy analyses based on change from period baseline will also be presented.

Because of the low expected power, a Bayesian analysis may be performed. The analysis will compute the posterior probability that the treatment difference is greater than 0, based on a non-informative prior distribution. There are no specific success criteria due to the low subject numbers available for analysis.

Data collected from subjects in Part 2 will be presented in subject listings. Summary statistics may also be provided.

IDMC Reviews

An Independent Data Monitoring Committee (IDMC) will be formed for this study. The IDMC will conduct regular, planned reviews of study data during Part 1 with the primary goal of evaluating the safety of the study drug regimen to ensure the subjects' safety. Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be included in the IDMC Charter. The IDMC Charter was finalized before the first subject was enrolled in the study. The IDMC Charter will be updated following approval of the protocol amendment to reflect changes impacted by the decision to terminate the study early.

3 SCHEDULE OF ASSESSMENTS

Table 3-1 Study VX15-770-123: Screening

Event/Assessment	Screening Period (Day -28 to Day -1)[a]
Clinic visit	X
Informed consent/assent	X
Inclusion/exclusion criteria review	X
Demography	X
CFTR genotype[b]	X
Medical history	X
Prior and concomitant medications	X
Height and weight	X
Physical examination and vital signs[c]	X
Multiple breath washout[d]	X
Coagulation	X
Serum chemistry	X
Hematology	X
Urinalysis	X
Ophthalmologic examinations[e]	X
Immunoreactive trypsinogen[f]	X
Fecal sample collection[g]	X
Adverse events	Continuous from signing of ICF through end of study participation

[a] All Screening assessments must be completed before the Day 1 Visit. Subjects may be rescreened after discussion with, and approval from, the Vertex medical monitor or authorized designee (see Section 8.1.1.2).

[b] *CFTR* genotyping will be performed to confirm that the subject has the *G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P,* or *G1349D* mutation in at least 1 *CFTR* allele to meet inclusion criteria. Results of the genotyping should be confirmed during the Screening Period. If the *CFTR* screening genotype result is not received before randomization, a previous *CFTR* genotype lab report may be used to establish eligibility. *Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study*.

[c] See Section 11.5.3.

[d] Subjects must complete the multiple breath washout (MBW) assessment at Screening. The subject will be considered a screen failure if the MBW assessment cannot be performed, i.e., if 2 technically acceptable MBW tests are not achieved at the Screening Visit (or Rescreening Visit; see Section 8.1.1.2.). At least 3 MBW tests will be performed (see Section 11.4.1 and the Study Reference Manual).

[e] An OE will be conducted by a licensed ophthalmologist or optometrist (Section 11.5.6). The examination does not need to be repeated if there is documentation of an OE meeting protocol criteria that was conducted within 3 months before the Screening Visit. Subjects with documentation of bilateral lens removal do not need the OE.

[f] A blood sample for immunoreactive trypsinogen assessment will be collected.

[g] A stool sample for fecal elastase-1 [redacted] analysis will be collected (see Sections 11.4.7 [redacted] for details). The stool sample to be collected at Screening may be collected at any time from Screening until before the first dose at Day 1.

Table 3-2 Study VX15-770-123: Part 1 and Part 2

	Part 1 Placebo-controlled Crossover Period[a]																
	Treatment Period 1 (Day 1 to Wk 8)			Wash-out	Treatment Period 2 (Wk 16 to Wk 24)			Part 2 Open-label Period[a] (Wk 24 to Wk 144)									
Event/ Assessment	Day 1	Wk 4 (± 3 days)	Wk 8 (± 5 days)	8 Wks (± 5 days)	Wk 16 (± 3 days)	Wk 20 (± 3 days)	Wk 24 (± 5 days)	Wk 36 (± 2 wks)	Wk 48 (± 2 wks)	Wk 60 (± 2 wks)	Wk 72 (± 2 wks)	Wk 84 (± 2 wks)	Wk 96 (± 2 wks)	Wk 108 (± 2 wks)	Wk 120 (± 2 wks)	Wk 132 (± 2 wks)	Wk 144 (± 2 wks)
Clinic visit	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria review	X																
Randomization[b]	X																
Concomitant medications	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant treatments and procedures	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Height and weight	X		X		X		X	X	X	X	X	X	X	X	X	X	X
Multiple breath washout[c]	X	X	X		X	X	X		X				X				X
[redacted]																	

Notes: Subjects may complete their assessments over a period of 2 days at the Day 1 and Week 96 Visits. On the Day 1, Week 16, and Week 24 Visits, all assessments must be completed before dosing with study drug. Symptom-directed physical examinations and symptom-directed vital signs can be performed if deemed necessary by the investigator or healthcare provider (see Section 11.5.3).

[a] Subjects who prematurely discontinue study drug treatment (for any reason other than early study termination) will undergo the listed assessments at their Early Termination of Treatment Visit (see Table 3-3), which is to be scheduled as soon as possible after the subject decides to terminate study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 4 weeks (± 7 days) after their last dose of study drug. If the Early Termination of Treatment Visit occurs 3 weeks or later following the last dose of study drug, then the Early Termination of Treatment Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required (see Section 8.1.7).

[b] Randomization will occur after all inclusion and exclusion criteria are met. If the screening genotype result is not received before randomization, a previous *CFTR* genotype lab report may be used to establish eligibility. *Subjects who have been randomized on the basis of a historical genotype lab report and whose screening genotype does not confirm study eligibility must be discontinued from the study.*

[c] At least 3 MBW tests will be performed (see Section 11.4.1 and the Study Reference Manual). [redacted]

Table 3-2 Study VX15-770-123: Part 1 and Part 2

	Part 1 Placebo-controlled Crossover Period[a]							Part 2 Open-label Period[a] (Wk 24 to Wk 144)								
	Treatment Period 1 (Day 1 to Wk 8)			Wash-out	Treatment Period 2 (Wk 16 to Wk 24)											
Event/ Assessment	Day 1	Wk 4 (± 3 days)	Wk 8 (± 5 days)	8 Wks (± 5 days)	Wk 16 (± 3 days)	Wk 20 (± 3 days)	Wk 24 (± 5 days)	Wk 36 (± 2 wks)	Wk 48 (± 2 wks)	Wk 60 (± 2 wks)	Wk 72 (± 2 wks)	Wk 84 (± 2 wks)	Wk 96 (± 2 wks)	Wk 108 (± 2 wks)	Wk 120 (± 2 wks)	Wk 132 (± 2 wks)	Wk 144 (± 2 wks)
Serum chemistry[e]	X		X		X		X	X	X		X		X				X
Hematology	X		X		X		X	X	X		X		X				X
Ophthalmologic examinations									X				X				X
Immunoreactive trypsinogen[f]	X		X		X		X		X				X				X
Fecal sample collection[g]			X		X		X		X				X				X
[redacted]																	

[redacted]

[e] Liver function testing (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltranspeptidase, alkaline phosphatase, and total bilirubin) must be performed at the scheduled visits and at a minimum of every 4 weeks only for subjects who meet protocol-defined criteria for study drug interruption or discontinuation (see Section 11.5.2). For these subjects, liver function tests (LFTs) must be monitored at least every 4 weeks and can return to monitoring at regularly scheduled study visits when LFT results have returned to the subject's baseline and remain at baseline values for 8 weeks. Although blood samples will be collected and analyzed at a central laboratory, a local laboratory may be used if a subject cannot return to the clinical study site for liver function testing (see Section 11.5.2).

[f] A blood sample for immunoreactive trypsinogen assessment will be collected.

[g] A stool sample for fecal elastase-1 [redacted] analysis will be collected (see Sections 11.4.7 [redacted] for details).

[redacted]

Table 3-2 Study VX15-770-123: Part 1 and Part 2

	Part 1 Placebo-controlled Crossover Period[a]							Part 2 Open-label Period[a] (Wk 24 to Wk 144)								
	Treatment Period 1 (Day 1 to Wk 8)			Wash-out	Treatment Period 2 (Wk 16 to Wk 24)											
Event/ Assessment	Day 1	Wk 4 (± 3 days)	Wk 8 (± 5 days)	8 Wks (± 5 days)	Wk 16 (± 3 days)	Wk 20 (± 3 days)	Wk 24 (± 5 days)	Wk 36 (± 2 wks)	Wk 48 (± 2 wks)	Wk 60 (± 2 wks)	Wk 72 (± 2 wks)	Wk 84 (± 2 wks)	Wk 96 (± 2 wks)	Wk 108 (± 2 wks)	Wk 120 (± 2 wks)	Wk 132 (± 2 wks)	Wk 144 (± 2 wks)
Meal or snack at study center[i]	X	X	X		X	X	X		X				X				X
Study drug dosing at study visit[i]	X	X	X[j]		X	X	X[k]		X				X				X
Dispense study drug[l]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	
Study drug count	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																	
Adverse events	Continuous from signing of ICF through end of study participation																

[i] Study drug (placebo or Kalydeco) will be administered from Day 1 to the dose before the planned Week 24 Visit. Study drug should be administered every 12 hours, with fat-containing food (see Section 10.2). At the scheduled visits indicated, this meal or snack will be provided at the clinic to subjects after all predose assessments have occurred. Although subjects will not be dosed with study drug at the Week 8 or Week 144 Visits, a meal or snack will be provided. All subjects will be treated with Kalydeco during Part 2.

[j] Study drug will not be administered at the Week 8 Visit of Treatment Period 1. The last dose of study drug in Treatment Period 1 is the dose of study drug before the Week 8 Visit.

[k] The first dose of Kalydeco in the Open-label Period will be administered at the Week 24 Visit. Kalydeco dosing will continue to the dose before the planned Week 144 Visit.

[l] Study drug will be assigned through an interactive voice or web response system.

Table 3-3 Study VX15-770-123: Early Termination of Treatment Visit, Safety Follow-up Visit, and Follow-up Telephone Contact

Event/Assessment	Early Termination of Treatment Visit[a]	Safety Follow-up Visit 4 weeks (±7 days) After Last Dose of Study Drug[a]	Follow-up Telephone Contact 4 weeks (±7 days) After the Week 144 Visit
Clinic visit	X	X	
Telephone Contact			X
Concomitant medications	X	X	
Concomitant treatments and procedures	X	X	
Height and weight	X	X	
Serum chemistry	X	X	
Hematology	X	X	
Ophthalmologic examinations[b]	X		
[redacted]			
Study drug count	X		
[redacted]			
Adverse events	Continuous from signing of ICF through end of study participation		

Note: Symptom-directed physical examinations and symptom-directed vital signs can be performed if deemed necessary by the investigator or healthcare provider (see Section 11.5.3).

[a] If the subject prematurely discontinues study drug treatment (for any reason other than early study termination), an Early Termination of Treatment Visit should be scheduled as soon as possible after the subject decides to terminate study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 4 weeks (± 7 days) after their last dose of study drug. If the Early Termination of Treatment Visit occurs 3 weeks or later following the last dose of study drug, then the Early Termination of Treatment Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required (see Section 8.1.7).

[b] Subjects who discontinue study drug treatment will have an OE that is to occur between their last dose of study drug and completion of the Early Termination of Treatment Visit.

[redacted]

4 TABLE OF CONTENTS

List of Tables

List of Figures

5 INTRODUCTION

5.1 Overview of Cystic Fibrosis

Cystic fibrosis (CF) is a chronically debilitating autosomal recessive disease with high morbidity and premature mortality that affects approximately 30,000 individuals in the United States[1] and 36,000 in the European Union (EU).[2] The disease affects predominately Whites[3] 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.[4] 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.[5] 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.[1,3] Currently, there is no cure for CF, and, despite adjunctive treatments with nutritional supplements, antibiotics, and mucolytics,[6] the median predicted age of survival of individuals born today with CF is approximately 40 years of age.[1,7]

More than 1900 mutations in the *CFTR* gene have been identified.[8] Analysis of *CFTR* gene mutations suggests that impaired CFTR protein function in airway epithelia is highly correlated with severity of lung disease in patients with CF and supports the hypothesis that restoration of CFTR protein activity would stop or slow the decline in lung function and extend life expectancy.[9,10] The most prevalent mutation is an in-frame deletion resulting in a loss of phenylalanine 508 (*F508del-CFTR*).[11] While the predominant effect of the *F508del* gene mutation is a severe decrease in the amount of CFTR trafficked to the cell surface, the mutation also results in defective CFTR channel opening.[11] A defect in channel opening is also a characteristic of *G551D-CFTR* (a missense mutation that results in the replacement of a glycine residue at position 551 of CFTR with an aspartic acid residue),[12] but, unlike F508del-CFTR, G551D-CFTR is delivered to the cell surface in normal amounts. *CFTR* gene mutations, like *G551D*, in which the primary defect is reduced channel opening, are known as *CFTR* gating mutations. *CFTR* gating mutations can be defined as *CFTR* mutations that result in the production of a CFTR protein for which the predominant defect is a low channel open probability compared to normal CFTR.[13]

One approach to increasing the level of chloride transport through the CFTR channels is to treat with a potentiator, a compound that increases the channel gating activity of CFTR protein located at the cell surface, resulting in increased chloride transport.[13,14] Potentiators represent a therapeutic strategy to treat CF. A modest restoration of chloride secretion through the action of a potentiator could prevent the hyperabsorption of water across the apical surface of epithelial cells, allowing for proper maintenance of airway hydration. Adequate airway hydration could alleviate the cycle of mucus plugging, infection, and inflammation that leads to irreversible structural changes in the lungs, and eventually respiratory failure for patients with CF.

5.2 Overview of Ivacaftor

Ivacaftor (Kalydeco®) is an orally administered CFTR potentiator that increases the channel-open probability of CFTR protein to enhance chloride transport, which yields clinical benefit in patients with CF. Globally, Kalydeco is indicated for the treatment of CF in patients as

young as 2 years who have the *G551D* and certain other gating mutations as well the *R117H* mutation in the *CFTR* gene depending on the country.

Results from Phase 3 studies (VX08-770-102 [Study 102] and VX08-770-103 [Study 103]) showed that ivacaftor is effective in the treatment of subjects with CF and the *G551D-CFTR* mutation aged 6 years and older, as evidenced by sustained improvements in CFTR channel function (measured by reduction in sweat chloride concentration) and corresponding substantial, durable improvements in lung function, pulmonary exacerbations, respiratory symptoms, and weight gain. Ivacaftor was also well tolerated, as evidenced by the rates and reasons for premature discontinuation and results of safety assessments. Similar results were observed in Study VX12-770-111 (Study 111) in subjects with CF aged 6 years and older with one of the following *CFTR* gating mutations: *G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*. Results from Study VX10-770-106 (Study 106) demonstrated that subjects with CF aged 6 years and older who were treated with ivacaftor can show improvements in lung function as measured by lung clearance index (LCI).

A Phase 3 study (VX11-770-108 [Study 108]) was conducted to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics of ivacaftor 50- and 75-mg doses in subjects with CF aged 2 through 5 years with a *CFTR* gating mutation. The safety results demonstrated that ivacaftor was well tolerated in subjects; the PK profile of the 50- and 75-mg doses of ivacaftor was similar to that of the 150-mg dose of ivacaftor in adults, thereby, demonstrating no significant differences in exposure, and there were clinically relevant improvements in sweat chloride (pharmacodynamic measure), nutritional status, and pancreatic function throughout a 24-week treatment period. These positive safety, PK, and efficacy results were sustained over an additional 84 weeks of treatment with ivacaftor in open-label rollover Study VX11-770-109 and efficacy measures remained above the Study 108 baseline throughout the duration of that study. Together, these data support the use of ivacaftor in children 3 through 5 years of age with CF.

5.3 Rationale for Present Study

The manifestations of CF begin as early as infancy, including airway inflammation, growth impairment, and evidence of structural lung damage that precedes a loss of pulmonary function as measured by forced expiratory volume in 1 second (FEV_1). Without early intervention, CF in young patients will lead to progressive, and in some cases irreversible, decline in nutritional and pulmonary status, increased hospital admissions, and reduced life expectancy. Studies of children with CF 1 month through 6 years of age have shown the presence of structural lung disease on computed tomography (CT) scans at an early age.[15] There are no data specifically describing lung disease in patients younger than 6 years of age who have a *CFTR* gating mutation; however, data from subjects who participated in Study 103 (*G551D-CFTR* mutation in at least 1 allele) who were 6 years of age suggest that some subjects had already developed lung disease and had nutritional complications of CF by that age. While the percentage of all patients with CF and the *G551D* or other gating mutation for subjects younger than 6 years of age sharing these characteristics were unknown, these data demonstrate that at least a proportion of subjects develop pulmonary and nutritional complications of CF before 6 years of age.

Data in the literature suggest that early therapeutic intervention is beneficial to young children with CF.[16] Although few studies have been done to evaluate the effect of therapies in children with CF younger than 6 years of age, studies have demonstrated benefits such as improved measures of growth, nutrition, and lung disease through early intervention in children diagnosed

by newborn screening.[17] Compounds such as CFTR modulators may have the potential to preserve normal lung and pancreatic exocrine function and to modify the course of disease progression. For example, results from long-term treatment with ivacaftor in patients with the *G551D* mutation show that increasing CFTR function can slow the rate of FEV_1 decline. Ivacaftor reduced the slope of percent predicted FEV_1 by about 50% compared to a homozygous *F508del* control population from the US CF Foundation registry demonstrating the sustained benefits of ivacaftor treatment and suggesting that modulating CFTR function can modify the course of disease in patients with CF.[18]

The results from Study 108 showed that ivacaftor (50- and 75-mg doses) was well tolerated and that there were clinically relevant improvements in sweat chloride, nutritional status, and pancreatic function throughout a 24-week treatment period in young subjects with CF with a gating mutation on at least 1 allele. Study VX15-770-123 (Study 123) will evaluate the efficacy of ivacaftor in this age range with respect to lung function as measured by LCI [redacted]. Pancreatic function as assessed by fecal elastase-1 and immunoreactive trypsinogen will also be evaluated.

Since spirometry is challenging for children younger than 5 years of age and results are variable, the efficacy of ivacaftor on lung function will be evaluated by using 2 methods: LCI, a measure of ventilation inhomogeneity that is based on tidal breathing techniques that have been evaluated in patients as young as infants,[19,20] [redacted] to determine structural lung abnormalities and to monitor disease progression.

The present study is designed to obtain long-term efficacy and safety information in this young age group to further understand the impact of ivacaftor on lung and pancreatic function. The study will also examine how long-term treatment with ivacaftor impacts the course of CF disease progression.

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the efficacy of ivacaftor treatment, as measured by LCI, in subjects with CF who have a specified *CFTR* gating mutation and are 3 through 5 years of age at the start of the study

6.2 Secondary Objectives

To evaluate the following in subjects with CF have a specified *CFTR* gating mutation and are 3 through 5 years of age at the start of the study:

- [redacted]
- Disease progression as measured by changes in pancreatic function
- The safety of ivacaftor treatment

7 STUDY ENDPOINTS

7.1 Part 1

7.1.1 Primary Endpoint

- Absolute change from baseline in $LCI_{2.5}$ through 8 weeks of treatment

7.1.2 Secondary Endpoints

- Absolute change from baseline in serum levels of immunoreactive trypsinogen at 8 weeks of treatment
- Absolute change from baseline in fecal elastase-1 at 8 weeks of treatment
- Absolute change from baseline in weight at 8 weeks of treatment
- Absolute change from baseline in body mass index (BMI) at 8 weeks of treatment
- Safety, as determined by AEs, clinical laboratory values (including LFTs), ophthalmologic examinations (OEs), physical examinations, and vital signs

[redacted]

7.2 Part 2

[redacted]

[redacted]

8 STUDY DESIGN

8.1 Overview of Study Design

This is a Phase 3b, 2-part, randomized, double-blind, placebo-controlled, crossover study with a long-term open-label period of orally administered ivacaftor in subjects with CF, aged 3 through 5 years at the start of the study, who have 1 of the following specified *CFTR* gating mutations on at least 1 allele: *G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P,* or *G1349D*. Approximately 50 subjects will be enrolled.

Subjects will be randomized 1:1 to receive 1 of 2 treatment sequences during Part 1:

- Sequence 1: ivacaftor in Treatment Period 1→washout→placebo in Treatment Period 2
- Sequence 2: placebo in Treatment Period 1→washout→ ivacaftor in Treatment Period 2

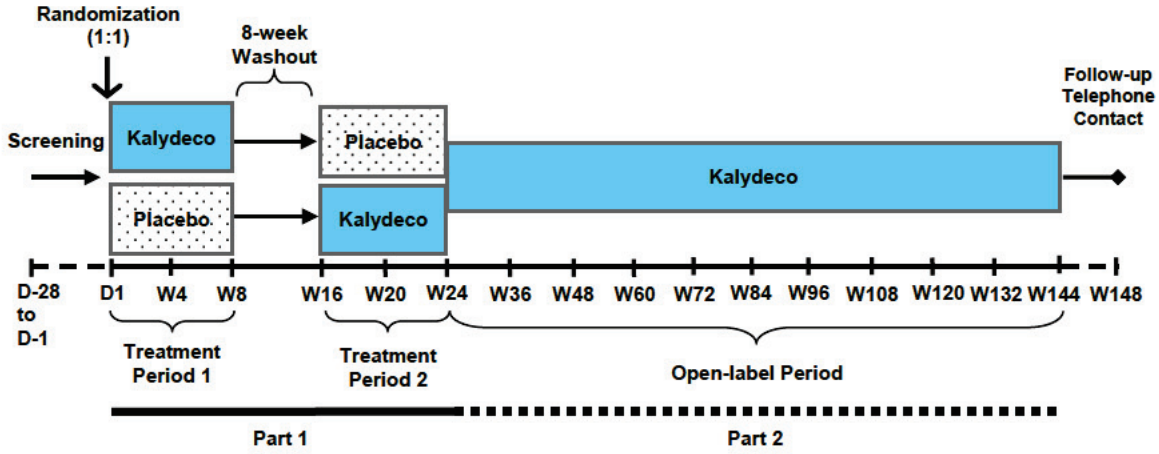
During Part 1, subjects will receive 50-mg or 75-mg ivacaftor (by weight, see Section 8.2.2) or placebo every 12 hours (q12h) for 16 weeks of treatment.

During Treatment Period 1 (Day 1 through Week 8), approximately 25 subjects will be dosed with placebo and approximately 25 subjects will be dosed with ivacaftor. During Treatment Period 2 (Week 16 through Week 24), subjects who were dosed with ivacaftor in Treatment Period 1 will be dosed with placebo, and subjects who were dosed with placebo will be dosed with ivacaftor.

Part 2 will be open-label and will continue to use weight-appropriate dosing; subjects may therefore be treated with 150-mg ivacaftor q12h. After completion of Part 1, subjects will immediately begin Part 2; there is no washout period in between Parts 1 and 2.

The study design is depicted in Figure 8-1.

Figure 8-1 Schematic of Study Design VX15-770-123



D: Day; W: week.

This study includes:

- Screening Period: Day -28 to Day -1 relative to the first dose of study drug
- Part 1 Treatment Period 1 through Treatment Period 2
  - Treatment Period 1: Day 1 (first dose of study drug) through Week 8
  - 8-week Washout Period
  - Treatment Period 2: Week 16 through Week 24
- Part 2 Open-label Period:
  - Week 24 through Week 144 (the first dose of ivacaftor during the Open-label Period will be given after completion of assessments at the Week 24 Visit); the Week 24 Visit (Part 1) is also considered the first visit of the Open-label Period.
- Follow-up Telephone Contact (4 weeks [± 7 days] after the last dose of study drug)
- Early Termination of Treatment Visit (which is to occur as soon as possible after the subject decides to terminate study drug treatment)

Following a review of study enrollment and assessment of the available number of potential subjects for this study, Vertex decided to close enrollment as of 21 February 2017 and withdraw subjects in order to terminate the study. After the protocol amendment has been approved at a site:

- Subjects in Part 1 of the study will be withdrawn from the study at their Week 24 Visit.
- Subjects in Part 2 will be withdrawn from the study and requested to complete the Early Termination of Treatment Visit. Subjects who have been treated with open-label ivacaftor for <4 weeks in Part 2 are not required to complete an ophthalmologic examination at their Early Termination of Treatment Visit.

- Safety Follow-up Visit for subjects who prematurely discontinue study drug treatment (approximately 4 weeks (± 7 days) after their last dose of study drug).
    - A Safety Follow-up Visit will not be required of subjects withdrawn from the study due to early study termination.

Study assessments are presented in Table 3-1, Table 3-2, and Table 3-3.

Maintenance of Stable Medication Regimen for CF:

During Part 1, it is recommended that subjects remain on stable CF medication regimens from 4 weeks before Day 1 through the Week 24 Visit. A stable medication regimen is defined as the current medication regimen that the subjects have 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 of Treatment Period 1 and on Weeks 16 and 24 of Treatment Period 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.

In Part 2, it is recommended that subjects maintain stable CF medication regimens through the end of the study.

8.1.1 Screening Period

Screening will occur within 28 days before administration of study drug. The investigator (or an appropriate authorized designee at the investigator site) will obtain informed consent from the subject's parent or legal guardian and assent from each subject (as applicable).

Subjects must complete the MBW assessment at Screening. The subject will be considered a screen failure if an MBW assessment cannot be performed, i.e., 2 technically acceptable MBW tests are not achieved at the Screening Visit (or Rescreening Visit; see Section 8.1.1.2)

8.1.1.1 Repetition of Screening Period Assessments

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

- There is clear evidence of a laboratory error (e.g., hemolyzed sample) or equipment malfunction. In this case, collection of a repeat sample for the appropriate laboratory test may be permitted after discussion with the Vertex medical monitor or authorized designee.

- If a convincing alternative etiology is identified for elevated transaminases, exclusionary liver function test (LFT) levels may be retested within 14 days of the original Screening Visit date.
- The MBW assessment cannot be performed.

If repeat values are within the eligibility criteria and completed within the Screening Period window, the subject is eligible for the study.

8.1.1.2 Rescreening

Subjects may be rescreened after discussion with, and approval from, the Vertex medical monitor or authorized designee. If a subject is rescreened, all Screening Visit assessments will be repeated except for CF genotyping and the OE (if the OE was performed within the last 3 months before the Rescreening Visit). If a subject is rescreened, the screening window will begin once the first rescreening assessment has been initiated.

8.1.1.3 Extension of Screening Period Window

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

- Repetition of Screening Period assessments (Section 8.1.1.1)
- Unexpected operational or logistic delays, or to meet the eligibility criteria
- Scheduling of the OE (Section 11.5.6)
- Availability of required equipment

8.1.2 Part 1: Treatment Period 1 (8 Weeks)

The first dose of study drug will be administered in Part 1 on Day 1. Study drug should be taken according to instructions provided. Study visits will occur on Day 1, Week 4, and Week 8. The last dose of study drug in Treatment Period 1 is the dose of study drug before the planned Week 8 Visit.

8.1.3 Part 1: Washout Period (8 Weeks)

Subjects will undergo a Washout Period of 8 weeks (± 5 days).

8.1.4 Part 1: Treatment Period 2 (8 Weeks)

The first dose of study drug in Treatment Period 2 will be administered at the Week 16 Visit after completing the Week 16 assessments. Study drug should be taken according to instructions provided. In order to continue into 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 Week 16 Visit (first dose of study drug in Treatment Period 2) and must not have any "non-CF-related" illness within 2 weeks before the Week 16 Visit (first dose of study drug in Treatment Period 2). "Illness" is defined as an acute (serious or non-serious) condition (e.g., gastroenteritis). If the subject does not meet these criteria, then the continuation of the subject into Treatment Period 2 should be discussed with the Vertex medical monitor. The last dose of study drug in Treatment Period 2 is the dose of study drug before the planned Week 24 Visit. Study visits will occur on Weeks 16, 20, and 24.

Following a review of study enrollment and assessment of the available number of potential subjects for this study, Vertex decided to close enrollment and terminate the study early. After the protocol amendment has been approved at a site, subjects in Part 1 will be withdrawn from the study at their Week 24 Visit (see Section 8.1).

8.1.5 Part 2: Open-label Period

The first dose of open-label ivacaftor will be administered at the Week 24 Visit after completion of the Week 24 assessments. The last dose of ivacaftor will be administered before the planned Week 144 Visit. The dose of ivacaftor (50 mg, 75 mg, or 150 mg) will be based on the subject's weight (see Section 8.2.2). Study visits will occur on Weeks 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, and 144.

Vertex decided to close enrollment and terminate the study early. After the protocol amendment has been approved at a site, subjects in Part 2 will be withdrawn from the study and requested to complete the Early Termination of Treatment Visit (see Section 8.1).

8.1.6 Follow-up Telephone Contact

A Follow-up Telephone Contact is scheduled to occur 4 weeks (± 7 days) after the Week 144 Visit for subjects who complete this visit. A Follow-up Telephone Contact is not required for subjects who have an Early Termination of Treatment Visit.

8.1.7 Early Termination of Treatment

Subjects who prematurely discontinue study drug treatment in Study 123 (for any reason other than early study termination) will be required to complete the Early Termination of Treatment Visit, which is to be scheduled as soon as possible after it is decided that the subject will terminate study drug treatment. Subjects who prematurely discontinue study drug treatment will also be required to complete the Safety Follow-up Visit, approximately 4 weeks (± 7 days), after their last dose of study drug. The assessments performed at the Safety Follow-up Visit are listed in Table 3-3.

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

Subjects will continue to complete all other scheduled study visits for assessments of efficacy and other endpoints as detailed in the Schedule of Assessments (see Section 3).

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

Subjects who discontinue study drug treatment during Part 1 will not be allowed receive study drug treatment in Part 2 of the study but will continue to complete the assessments of efficacy as described above.

After the protocol amendment has been approved at a site, subjects in Part 1 will be withdrawn from the study at their Week 24 Visit, and subjects in Part 2 will be withdrawn from the study and requested to complete the Early Termination of Treatment Visit (see Section 8.1).

8.1.8 Safety Follow-up Visit

Subjects who prematurely discontinue study drug treatment (for any reason other than early study termination) will have a Safety Follow-up Visit, approximately 4 weeks (± 7 days) after their last dose of study drug. If the Early Termination of Treatment Visit occurs 3 weeks or later following the last dose of study drug, then the Early Termination of Treatment Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required. Safety Follow-up assessments are listed in Table 3-3.

8.1.9 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be formed for this study. The IDMC will conduct regular, planned reviews of study data during Part 1 with the primary goal of evaluating the safety of the study drug regimen to ensure the subjects' safety (Section 12.3.5). Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be included in the IDMC Charter. The IDMC Charter was finalized before the first subject was enrolled in the study. The IDMC Charter will be updated following approval of the protocol amendment to reflect changes impacted by the decision to terminate the study early.

8.2 Rationale for Study Design and Study Drug Regimens

8.2.1 Study Design

This Phase 3b, 2-part, randomized, double-blind, placebo-controlled, crossover study with a long-term open-label follow-on period is designed to evaluate the efficacy and safety of ivacaftor in subjects with CF, aged 3 through 5 years at the start of study, who have 1 of the following *CFTR* gating mutations on at least 1 allele: *G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P,* or *G1349D.*

CF pulmonary disease progresses throughout life. However, it is not uncommon for young patients with CF to have well-preserved or even normal lung function as measured by spirometry.[21-24] In spite of the potentially normal lung function, patients in this age group with severe CF-causing mutations likely already have pulmonary structural aberrations [redacted].[24-29] Consistent with these observations, impaired LCI, which measures the degree of small airway disease by assessing ventilation inhomogeneity, can be observed in pediatric patients with normal lung function as measured by spirometry. These observations confirm that the disease process that results from a lack of CFTR activity begins early in life and before lung function, as assessed by spirometry, is affected.

Unlike previous studies with ivacaftor in this age group (e.g., Study 108), which focused on the safety and PK of ivacaftor, Study 123 will evaluate the efficacy of ivacaftor using endpoints that are consistent with the natural history of disease course in this age group; these include LCI, [redacted] and measures of pancreatic function:

- Changes in LCI have been observed in advance of deterioration of lung function as assessed by spirometry.[30,31] In Study 106, subjects aged 6 years and older with CF and the *G551D* mutation who had well-preserved lung function (FEV_1 >90% predicted) demonstrated significant improvements in lung function as assessed by LCI during treatment with ivacaftor. In Study 123, LCI will be evaluated both during the Placebo-controlled Crossover Period and during the long-term Open-label Period.

- Changes in lung structure have been observed in advance of deteriorations in spirometry.[29] Progression of structural aberrations has been associated with clinical progression of pulmonary disease. Preliminary results suggest that ivacaftor treatment in an adult population may halt progression or even improve structural damage in patients aged 10 and older.[32] As subjects in Study 123 are expected to have early and developing structural damage, intervention with ivacaftor during this stage of development may have a significant impact on the development and progression of structural defects. [redacted]. Given exposure to ionizing radiation during this procedure and the expected timing of a treatment effect, a treatment effect for CT will not be evaluated during the placebo-controlled crossover phase but will be assessed by a within-group comparison between study baseline and the Week 96 Visit.
- Results from Study 108 suggest that ivacaftor treatment in this age group improves pancreatic function as assessed by fecal elastase-1 and serum immunoreactive trypsinogen. To examine this further, the impact of ivacaftor on pancreatic function will be evaluated in Study 123 during both the Placebo-controlled Crossover Period and the Open-label Period; results of these measures during the Placebo-controlled Crossover Period will facilitate evaluation of the hypothesis that ivacaftor yields clinically meaningful improvements in pancreatic function.

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 LCI and markers of pancreatic function. In addition to the increased power of a crossover study design in this study with a limited population of potential subjects with varied genotypes, the design provides a period of both active and placebo treatment to allow evaluation of the efficacy and safety of ivacaftor in subjects with CF with the selected gating mutation genotypes enrolled in the study. Given the intent to try to demonstrate efficacy with respect to LCI, which is still an endpoint under evaluation in this age group, the use of placebo is necessary in order to provide a robust assessment. It is considered justified since all subjects within the relevant country are expected to be recruited before ivacaftor granules are available commercially. The placebo or active drug will be added to the current standard of care, and no therapies are required to be withdrawn. Therefore, no subject will be disadvantaged by the use of placebo in 1 treatment period, and all will have the potential to benefit in the other treatment period and the Open-label Period when they will receive ivacaftor.

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

Examination of the efficacy and safety of ivacaftor over the course of the long-term Open-label Period in this younger CF population will provide information about disease progression.

Following a review of study enrollment and assessment of the available number of potential subjects for this study, Vertex decided to close enrollment as of 21 February 2017 and withdraw subjects in order to terminate the study (see Section 8.1).

8.2.2 Study Drug Dose and Duration

During Part 1 (Placebo-controlled Crossover Period), subjects will be randomized to receive ivacaftor or placebo q12h during Treatment Periods 1 and 2; the total study drug treatment duration is 16 weeks.

Subjects will receive ivacaftor during Part 2 (Open-label Period); if Part 2 is completed, the total duration of ivacaftor treatment will be 120 weeks.

After the protocol amendment has been approved at a site, subjects in Part 1 will be withdrawn from the study at their Week 24 Visit, and subjects in Part 2 will be withdrawn from the study and requested to complete the Early Termination of Treatment Visit (see Section 8.1).

Subjects weighing <14 kg on Day 1 will be administered 50-mg ivacaftor q12h, and subjects weighing ≥14 kg to <25 kg on Day 1 will be administered 75-mg ivacaftor q12h. The dose may be adjusted at the start of Part 1 Treatment Period 2 (i.e., the Week 16 Visit), if needed, such that subjects continue to receive the weight-appropriate dose. Note: the dose of study drug administered on Day 1 of Treatment Period 1 and at the start of Treatment Period 2 (i.e., the Week 16 Visit) will not change during the respective treatment period.

In Part 2, the subject's weight will be assessed on an ongoing basis and the ivacaftor dosage will be modified accordingly; subjects who become ≥14 kg during the course of the study will receive 75-mg ivacaftor q12h, and subjects who become ≥25 kg during the course of the study will receive 150-mg ivacaftor q12h. Therefore, it is likely that the dose will be adjusted during the study such that subjects will continue to receive the weight- appropriate dose.

8.2.3 Rationale for Study Assessments

The following assessments are widely accepted and generally recognized as reliable, accurate, and relevant to the study of patients with CF.

LCI: LCI is a measure of ventilation inhomogeneity derived from MBW assessments that is based on tidal breathing techniques that has been evaluated in patients as young as infants.[19,20] 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.[27,31] Furthermore, data from Study 106 in CF patients 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 during the early stages of disease progression, 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 saving time and sensitivity.[33] [redacted]

[redacted]

Measures of Nutritional Status: Poor somatic growth and poor nutritional status are common in patients with CF owing to a number of factors, including increased energy expenditures and

appetite suppression due to lung disease, as well as diabetes and pancreatic insufficiency-related fat malabsorption.[35] Malnutrition is associated with worsening lung function in children with CF and is also an independent predictor of mortality in children with CF.[36]

While it is unknown if poor weight gain predicts clinical lung disease or whether progressive lung disease leads to poor weight gain, change in weight is a clinically relevant endpoint. Given that ivacaftor is a systemic therapy, it has the potential to improve extrapulmonary manifestations of CF. Modulation of CFTR function in the pancreas and gastrointestinal tract may lead to improvements in digestion and, consequently, weight gain.

In the Phase 3 studies of ivacaftor, the improvement in mean weight gain after 24 weeks of ivacaftor versus placebo treatment was substantial, clinically meaningful, and statistically significant (Ivacaftor Investigator's Brochure).

As children gain weight as part of normal growth, adjustment for age and sex is necessary to assess changes in nutritional status in a population of boys and girls in varying stages of growth. [redacted] Weight and height will be collected at the study visits indicated in the schedule of assessments above (Section 3).

[redacted]

In the Phase 3 studies of ivacaftor in subjects with CF who have a *CFTR* gating mutation, treatment with ivacaftor led to a substantial and statistically significant improvement in lung function, as measured by FEV_1.

Measures of Pancreatic Function: Fecal elastase-1 is used clinically to diagnose pancreatic exocrine insufficiency in patients with CF. The increasing use of fecal elastase-1 in the clinic is a result of the relative ease of collecting samples for its assessment and the establishment of diagnostic cut-offs for pancreatic exocrine function.[49-53] Therefore, fecal elastase-1 represents a

feasible measure to evaluate exocrine pancreatic function in this study. Immunoreactive trypsinogen is a serum-based marker of pancreatic insufficiency and will be collected at multiple time points during the study to allow further evaluations of changes in exocrine pancreatic function during the treatment period.[54]

[redacted]

9 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.

9.1 Inclusion Criteria

1. Male or female with confirmed diagnosis of CF, defined as:

   o a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis

   OR

   2 CF-causing mutations (all as documented in the subject's medical record)

   AND

   o Clinical manifestations of CF

2. Must have 1 of the following *CFTR* gating mutations on at least 1 allele: *G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P,* or *G1349D*. If the *CFTR* screening genotype result is not received before randomization, a previous *CFTR* genotype lab report may be used to establish eligibility. *Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study as described in Section 9.4.*
3. Subjects will be between the ages of 3 and 5 years, inclusive, at Screening and Day 1.
4. Weight ≥8 kg to <25 kg at Screening and Day 1
5. Hematology, serum chemistry, and coagulation at Screening with no clinically significant abnormalities or concomitant diagnosis that would interfere with the LCI and CT scan study assessments, as judged by the investigator.
6. Parent or legal guardian must sign the informed consent form (ICF) and corresponding assent must be obtained from the subject, as applicable.
7. As judged by the investigator, parent or legal guardian must be able to understand protocol requirements, restrictions, and instructions and the parent or legal guardian should be able to ensure that the subject assents to participation in the study to the degree the subject can assent, and that the subject will comply with and is likely to complete the study as planned.

9.2 Exclusion Criteria

1. History of any illness or condition that, in the opinion of the investigator, might confound the results of the study, impact use of the LCI or CT scan as assessments or pose an additional risk in administering study drug to the subject
2. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before Day 1
3. Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject (in the opinion of the investigator)
4. Abnormal liver function, at Screening, defined as ≥3 × upper limit of normal (ULN), of any 3 or more of the following: serum aspartate transaminase (AST), serum alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT), serum alkaline phosphatase (ALP), and total bilirubin
5. History of solid organ or hematological transplantation
6. Any clinically significant "non-CF-related" illness within 2 weeks before Day 1. "Illness" is defined as an acute (serious or nonserious) condition (e.g., gastroenteritis)
7. Use of any moderate or strong inducers or inhibitors of cytochrome P450 (CYP) 3A within 2 weeks before Day 1
8. Participation in a clinical study involving administration of either an investigational or a marketed drug within 30 days or 5 terminal half-lives (whichever is longer or as determined by the local requirements) before Screening

9.3 Prior and Concomitant Medications

Information regarding all prior and concomitant medications, including the subject's CF medications, other medications, and herbal and naturopathic remedies (including drug name, dose, and dose regimen) administered from Screening through the end of study participation will be collected.

It is recommended that subjects remain on their medication regimens for their CF from Day 1 through the end of study participation.

Use of short-acting and long-acting bronchodilators will be recorded in the source documents.

Subjects must not use moderate or potent CYP3A inhibitors and inducers including certain herbal medications and grapefruit/grapefruit juice through the end of study participation.

Subjects must not use commercially available ivacaftor (Kalydeco®) during the study.

A more comprehensive list of restricted medications will be provided in the Study Manual. Noncompliance with these restrictions will be addressed on a case-by-case basis with the Vertex medical monitor.

9.4 Removal of Subjects in the Study

Subjects may withdraw from the study at any time at their own request or at the request of the parent or legal guardian. Subjects may be withdrawn from study drug treatment at any time at the

discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons.

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

Subjects who discontinue study drug treatment early should continue to return for study assessments, as noted in Section 8.1.7.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject's parent or legal guardian. 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 8.1.7), and follow up with the subject regarding any unresolved 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.

A subject **will be** discontinued from the study for any of the following reasons:

- Vertex, regulatory authorities, or the site's Institutional Review Board (IRB) or Ethics Committee (EC) close the study
- A subject begins treatment with commercially available ivacaftor (Kalydeco)
- Subjects who are randomized on the basis of a historical genotyping result and whose screening genotype does not confirm eligibility.

A subject **will be** discontinued from study drug dosing for any of the following reasons:

- A subject has one of the following and no alternative etiology (e.g., viral hepatitis) for the elevated transaminase is identified, regardless of whether ALT or AST levels have improved (see Section 11.5.2):
  - An elevated ALT or AST of >8 × ULN, or
  - ALT or AST >5 × ULN for more than 2 weeks, or
  - An elevation of ALT or AST >3 × ULN in association with total bilirubin >2 × ULN and/or clinical jaundice
- A subject is noncompliant with study protocol requirements, restrictions, and instructions.
- A subject participates in another therapeutic clinical study.

A subject **may be** discontinued from the study, after discussion between the investigator and the Vertex medical monitor, for any of the following reasons:

- A subject develops a medical condition that requires prolonged concomitant therapy with a prohibited medication or prolonged interruption of ivacaftor.
- A subject develops a life-threatening AE or serious AE (SAE) that places them at immediate risk.

- A subject has an increase in LFTs (e.g., AST or ALT levels) to 3 × ULN (if LFTs are normal at baseline on Day 1) or an increase that exceeds an absolute value of 5 × ULN (regardless of whether LFTs are normal at baseline on Day 1).

If the subject is withdrawn from the study and the parent or legal guardian also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. Vertex may retain and continue to use any data collected before such withdrawal of consent.

Following a review of study enrollment and assessment of the available number of potential subjects for this study, Vertex decided to close enrollment and terminate the study early. After the protocol amendment has been approved at a site, subjects in Part 1 will be withdrawn from the study at their Week 24 Visit, and subjects in Part 2 will be withdrawn from the study and requested to complete the Early Termination of Treatment Visit (see Section 8.1).

9.5 Replacement of Subjects

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

10 STUDY DRUG ADMINISTRATION AND MANAGEMENT

10.1 Preparation and Dispensing

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

10.2 Administration

During Part 1, each 50- or 75-mg dose of ivacaftor will be provided as granules in a capsule. During Part 2, these doses will be provided as granules in a sachet.

The entire contents of each capsule or sachet of granules should be mixed with 1 teaspoon (5 mL) of age-appropriate soft food or liquid and completely consumed. Each dose should be administered just before or just after fat-containing food. Parents will be instructed on how to empty the capsules or sachets and administer ivacaftor with food. Details of dose preparation and dose administration will be provided in the Study Manual.

The 150-mg dose of ivacaftor will be provided as two 75-mg doses of ivacaftor in sachets. The 150-mg dose may also be provided as a tablet after discussion with the medical monitor. It is recommended that subjects take 150-mg dose of ivacaftor with fat-containing food. Examples of appropriate fat-containing foods will be described in the Study Manual.

Guidelines for ivacaftor administration are as follows:

- Ivacaftor should be administered q12h.
- Whenever possible, subjects should take ivacaftor at the same time each day. For example, the morning dose could be taken at 8:00 AM every morning and the evening dose could be taken at 8:00 PM every evening throughout the study.
- If subjects forget to take a dose and remember within 0 to 6 hours (before the halfway point of the dosing interval), they should take the dose at that time with fat-containing food and resume their normal schedule for the following dose.

- If subjects forget to take a dose and remember within 6 to 12 hours after the missed dose, they should skip that dose and resume their normal schedule for the following dose.

10.3 Method of Assigning Subjects to Treatment Groups

Part 1

Subjects will be considered enrolled when they are determined to have met all eligibility criteria and are randomized to a treatment sequence (Sequence 1 or Sequence 2). Subjects will be randomized in a 1:1 ratio.

An interactive voice response system (IVRS)/interactive web response system (IWRS) will be used to assign subjects to treatment. Detailed instructions for randomization and randomization code generation will be provided separately.

Part 2

Part 2 is open-label. Randomization is not required for Part 2 because all subjects will receive ivacaftor.

10.4 Dose Modification for Toxicity

Modifications of the ivacaftor doses are prohibited. Interruptions of study drug dosing should be discussed with the Vertex medical monitor and may be considered on a case-by-case basis after discussion with the Vertex medical monitor. Specific instructions for interruption for elevated LFTs are provided in Section 11.5.2.

10.5 Packaging and Labeling

For Part 1, the 50-mg or 75-mg doses of ivacaftor or placebo granules in a capsule will be supplied by Vertex in bottles. For Part 2, these doses will be supplied as granules in sachets. The film-coated ivacaftor tablet formulation (150 mg) will be supplied in child-resistant blister dosing cards. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for ivacaftor will be included in the pharmacy manual.

10.6 Study Drug Supply, Storage, and Handling

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. Storage and handling conditions will be provided in the pharmacy manual. The identity of study drug is presented in Table 10-1.

Table 10-1 Identity of Study Drugs

Dosage	Packaging	Formulation/ Route of Administration	Storage Condition
Placebo	Supplied as 50-mg or 75-mg capsules in bottles containing granules	Capsules containing granules/oral	Store at ≤25°C with excursions to 30°C
50-mg ivacaftor	Supplied as 50-mg capsules in bottles or sachets[a] containing granules	Capsules or sachets[a] containing granules/oral	Store at ≤25°C with excursions to 30°C
75-mg ivacaftor	Supplied as 75-mg capsules in bottles or sachets[a] containing granules	Capsules or sachets[a] containing granules/oral	Store at ≤25°C with excursions to 30°C
150-mg ivacaftor	• Supplied as two 75-mg sachets[a] • Supplied as 150-mg tablets (upon request)	• Sachets[a] containing granules/oral • Blue, film-coated tablet with wax/oral	Store at ≤25°C with excursions to 30°C

[a] To be specified in the pharmacy manual

10.7 Drug Accountability

The pharmacist or designated site staff will maintain information regarding the dates and amounts of (1) study drug received, (2) drug dispensed to the subjects, and (3) 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 until inventoried by the study monitor. The study monitor will review study drug records and inventory throughout the study.

10.8 Disposal, Return, or Retention of Unused Drug

The 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.

10.9 Compliance

Study drug accountability should be assessed at each visit by counting returned dosage units (tablets [150 mg] or capsules or sachets [50 mg and 75 mg]). Discrepancies should be discussed with the subject and recorded in the case report form (CRF).

If subjects demonstrate continued noncompliance with study requirements, restrictions, instructions, and study drug dosing despite educational efforts, the investigator should contact the Vertex medical monitor to discuss noncompliance and discontinuation of the subject from the study.

10.10 Blinding and Unblinding

10.10.1 Blinding

Part 1 is a double-blind study. The subjects and all site personnel, including the investigator and the study monitor, will remain blinded to treatment assignments until database lock. The Vertex study team will remain blinded to treatment assignments until all subjects have completed Part 1 of the study.

All study personnel will be blinded to subject treatment assignments except for the following individuals:

- 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
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations
- Unblinded statistician preparing the final (production) randomization list who is not part of the study team
- Vendor preparing the unblinded analysis for the IDMC
- Vertex Data Management IWRS management
- Vertex Clinical Supply Chain

LCI Data Blinding

Despite treatment blinding, knowledge of the LCI results has the potential to suggest whether a subject has been administered active study drug or placebo. Therefore, during Part 1, the Vertex study team will have no access to the post-dose LCI data.

10.10.2 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 Vertex 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 13.1.2.3.

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, Table 3-2, and Table 3-3.

11.2 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, and weight; and will be collected for each subject at the Screening Period.

In addition, the following historical data will be collected for each subject from birth to Screening: age at CF diagnosis, weight, height, hospitalizations, pulmonary exacerbations, LFTs, meconium ileus, and CF-related medications of interest. The following historical data from birth to Screening will also be collected:

- Fecal elastase-1, [redacted] and immunoreactive trypsinogen values, dates, and associated laboratory reference ranges
- Any elevation of ALT or AST >2 × ULN (yes or no); if yes, the ALT and/or AST values, dates, and associated laboratory reference ranges will be collected
- [redacted]

11.3 Pharmacokinetics

Not applicable

11.4 Efficacy

11.4.1 Lung Clearance Index

LCI is derived from N_2-MBW testing and will be conducted at visits specified in 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]

Each MBW will be performed in multiple replicates for each visit and the mean LCI value at each visit during Part 1 and Part 2 will be calculated using all technically acceptable washout

replicates. In order to derive mean LCI values, at least 3 MBW tests will be performed at each visit.

All LCI replicate values will be provided by a central reader, however, the LCI central reader will not perform the calculation for the mean LCI values at visits during Part 1 and Part 2. Thus, the mean LCI value at each Treatment Period visit will be calculated by the sponsor or sponsor designee from the technically acceptable values provided by the LCI central reader. Subjects must complete the LCI assessment at Screening. The subject will be considered a screen failure if the MBW assessment cannot be performed, i.e., if 2 technically acceptable MBW tests are not achieved at the Screening Visit (or Rescreening Visit; see Section 8.1.1.2).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] Subjects and parents/caregivers should not be informed of study-related LCI results.

Detailed MBW 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]

[redacted]

11.4.5 Measures of Nutritional Status

Weight and height be will measured at the time points noted in Table 3-1, Table 3-2, and Table 3-3. [redacted] Detailed procedures for measurement of weight and height will be provided in the Study Manual.

11.4.6 Immunoreactive Trypsinogen

Blood samples will be collected for immunoreactive trypsinogen at the time points noted in and Table 3-2. Specific instructions for the collection, processing, and shipment of samples will be provided in a separate Laboratory Manual.

11.4.7 Fecal Elastase-1

Stool samples for assessment of fecal elastase-1 will be collected at the time points noted in and Table 3-2. This sample may be collected at the study center during the study visit or may be collected by the subject at home and brought to the study visit. Specific instructions for the collection, storage, processing, and shipment of samples will be provided in a separate Laboratory Manual.

Note: A single stool sample for analysis of fecal elastase-1 is adequate.

[redacted]

11.5 Safety

Safety evaluations will include clinical laboratory assessments (including LFTs), OEs, and reporting of AEs.

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 CRF completion guidelines for investigators as well as training will be provided.

11.5.2 Clinical Laboratory Assessments

Blood samples will be collected at times specified in Table 3-1, Table 3-2, and Table 3-3 and will be analyzed at a central laboratory (Note: If, under exceptional circumstances, blood samples must be drawn and/or analyzed at a local laboratory, approval must first be obtained from the medical monitor). All blood samples will be collected while subjects are in a seated or supine position. Specific instructions for the collection, processing, and shipment of samples will be provided in a separate Laboratory Manual. Laboratory test results that are abnormal and considered clinically significant must be reported as AEs (see Section 13.1).

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

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis[a]
Glucose	Hemoglobin	Leukocytes
Blood urea nitrogen	Red blood cell count	Nitrite
Creatinine	Platelet count	Urobilinogen
Sodium	White blood cell count	Protein
Potassium	Differential (absolute and percent):	pH
Calcium	Eosinophils	Blood
Inorganic phosphate	Basophils	Specific gravity
Lactate dehydrogenase	Neutrophils	Ketones
Total protein	Lymphocytes	Bilirubin
Albumin	Monocytes	Glucose
Indirect bilirubin	**Coagulation Studies[a]**	
Amylase	Activated partial thromboplastin time	
Lipase	Prothrombin time	
Creatine kinase[a]	Prothrombin time International Normalized Ratio	
Liver Function Tests		
Alkaline phosphatase		
Aspartate transaminase		
Alanine transaminase		
Gamma-glutamyltransferase		
Total bilirubin		

[a] To be conducted at Screening only.

***CFTR* Genotype**:

CFTR genotyping will be performed to confirm the subject has the *G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P,* or *G1349D* mutation in at least 1 *CFTR* allele. Subjects who have been randomized on the basis of a historical genotype lab report and whose screening genotype does not confirm study eligibility must be discontinued from the study. Specific instructions will be provided in the Laboratory Manual.

Mandatory Liver Function Testing:

Liver function testing (ALT, AST, GGT, ALP, and total bilirubin) must be performed while subjects are receiving study drug treatment, according to the schedule of assessments, with the exception of subjects who meet protocol-defined criteria for study drug interruption or discontinuation below. For these subjects, LFTs must be monitored at least every 4 weeks as noted in Table 3-2, and can return to monitoring at regularly scheduled study visits when LFT results have returned to the subject's baseline and remain at baseline values for 8 weeks. These blood samples should be processed and shipped immediately per the Laboratory Manual.

If a subject cannot return to the site for liver function testing, a local laboratory may be used. Elevations in LFTs ≥2 × ULN at the local laboratory must be reported immediately to the Vertex 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).

It is strongly recommended that subjects with new ALT or AST elevations of >3 × ULN and clinical symptoms be followed closely, including repeat confirmatory testing within 48 to

72 hours of the initial finding and subsequent close monitoring of ALT and AST level, as clinically indicated.

As described in Section 9.4, it is recommended that an increase in LFTs to 3 × ULN (if LFTs are normal at baseline) or an increase that exceeds an absolute value of 5 × ULN (regardless of whether LFTs are normal at baseline) should be discussed with the Vertex medical monitor.

Study Drug Interruption or Discontinuation Due to Elevated Liver Function Test Parameters:

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

- ALT or AST >8 × ULN, or
- ALT or AST >5 × ULN for more than 2 weeks, or
- ALT or AST >3 × ULN in association with elevation of 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.

If no convincing alternative etiology (e.g., viral hepatitis) 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 Vertex medical monitor (see Section 9.4). Subjects discontinued for elevated transaminases should be followed until their transaminases normalize or return to baseline.

If a convincing alternative etiology for the elevated transaminases is identified and the subject's symptoms and laboratory findings have improved, the investigator may consider resuming study drug treatment in consultation with the Vertex medical monitor.

Additional Evaluations:

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests that a more detailed assessment of clinical laboratory safety evaluations is required. Any changes to the scheduled times of clinical laboratory determination will be agreed with Vertex and documented in the study master files.

11.5.3 Physical Examinations and Vital Signs

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

A physical examination includes a review of the following systems: head/neck/thyroid; eyes/ears/nose/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 physical examinations will be reported as AEs.

Vital signs include blood pressure (systolic and diastolic), temperature, heart rate, and respiration rate. These will be assessed following at least a 5-minute rest.

11.5.4 Electrocardiograms

Not applicable

11.5.5 Contraception and Pregnancy

Not applicable

11.5.6 Ophthalmologic Examinations

Subjects will undergo an OE at all time points indicated in, Table 3-1, Table 3-2, and Table 3-3. The OE will be conducted by a licensed ophthalmologist or optometrist, preferably a pediatric ophthalmologist.

The OE will include the following:

- measurement of best corrected distance visual acuity of each eye,
- measurement of lens refracting power (autorefractor or ophthalmoscopy streak following cycloplegia), and
- examination of the lens with a slit lamp.

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

- history of steroid use;
- history or presence of diabetes;
- any prior ophthalmologic or optometric examinations;
- history of trauma to the eye;
- any family history of glaucoma, congenital cataracts, or cataracts arising later in life;
- use of corrective lenses (contact lenses or eyeglasses);
- history of prolonged exposure to sunlight or ultraviolet light and use of sunglasses;
- history of exposure to secondhand smoke;
- history of radiation exposure (e.g., X-ray); and
- history of retinopathy of prematurity.

If an adequate slit-lamp examination cannot be conducted at the Screening OE, the subject will not be enrolled in Part 1 until an adequate repeat OE is completed (within 4 weeks). The Screening OE does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the Screening Visit. Subjects with documentation of bilateral lens removal do not need the OE.

If a visually significant lens opacity or cataract is identified at Screening, the Vertex medical monitor must be notified. Additional OEs may be required if a lens opacity or cataract is identified at Screening.

Subjects who discontinue from study drug treatment will have an OE that is to occur between their last dose of study drug and completion of the Early Termination of Treatment Visit.

12 STATISTICAL AND ANALYTICAL PLANS

Analysis of all data will be performed by Vertex (or its designee). A detailed analysis plan for the analysis of efficacy and safety data will be presented in the statistical analysis plan (SAP).

12.1 Sample Size and Power

It is planned that approximately 50 subjects will be enrolled in this study. As shown in Table 12-1, a sample size of 50 subjects will provide approximately 80% power to detect a treatment difference in mean change from study baseline in LCI (difference between ivacaftor and placebo in the change from study baseline) of 1.5 points. The calculation is based on a paired t-test with a 2-sided significance level of 0.05, and assumes that the within-subject standard deviation (SD) for the difference in change from study baseline for the 2 periods is 3.5 points, and that the dropout rate is about 10% for Part 1.

Different scenarios are presented in Table 12-1 for the variability and the magnitude of the treatment effect based on 80% power and 2-sided significance level of 0.05. The most conservative scenarios are presented in the last 2 rows of the table (i.e., treatment effect of 1.0 and 1.5, respectively).

Table 12-1 Sample Size Calculation Corresponding to Different Values of Treatment Effect on Lung Clearance Index Change-From-Predose

Treatment Effect (points) on LCI Change From Study Baseline	Standard Deviation of Paired Treatment Difference in LCI Change From Study Baseline	N
1.0	1.0	12
1.0	1.2	15
1.0	1.5	22
1.0	1.8	31
1.0	2.0	37
1.0	2.2	45
1.5	3.5	50

12.2 Analysis Sets

The **Full Analysis Set** (FAS) is defined as all randomized subjects who have a *G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P,* or *G1349D* mutation on at least 1 allele and who received at least 1 dose of study drug (i.e., ivacaftor or placebo) and had at least 1 post-baseline assessment. All non-safety (e.g., demographics) summaries will be referenced using the FAS, as appropriate. In the FAS, subjects will be analyzed according to the treatment sequence they were randomized to.

The **Safety Set** is defined as all subjects who received at least 1 dose of study drug. All summaries of safety will be referenced using the Safety Set, and will be performed per treatment received.

All subject data will be presented in the subject data listings.

12.3 Statistical Analysis

The primary objective of the study is to evaluate the efficacy of ivacaftor treatment in subjects with CF who have a specified *CFTR* gating mutation and who are 3 through 5 years of age at the start of the study, as measured by LCI.

This section presents a summary of the planned statistical analyses of efficacy and safety for this study. The Vertex Biometrics department or a designated CRO will analyze the data derived from this study. 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

The following summaries will be performed for Part 1:

- **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.

Baseline: For this crossover study, 2 types of baseline (study baseline and period baseline) will be defined for Parts 1 and 2.

For Part 1: The study baseline is defined as the most recent nonmissing measurement collected prior to the initial administration of study drug in Treatment Period 1. Period baseline is defined as the most recent nonmissing measurement collected before the initial 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.

For Part 2: The study baseline is defined as the most recent nonmissing measurement collected prior to the initial administration of study drug of Treatment Period 1. Period baseline is defined as follows:

- For Treatment Sequence 1 (ivacaftor→washout→placebo), period baseline will be defined as the most recent nonmissing measurement collected prior to initial administration of ivacaftor in the Open-label Period (Part 2).
- For Treatment Sequence 2 (placebo→washout→ivacaftor), period baseline will be the same as period baseline for Treatment Period 2 in Part 1 (i.e., the Week 16 Visit).

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.

Data collected from subjects in Part 2 will be presented in subject listings. Summary statistics may also be provided.

12.3.2 Background Characteristics

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, study drug exposure and compliance, and other background characteristics will be

summarized. All summaries will be based on the FAS, unless otherwise specified in the SAP and will be performed separately by data in Parts 1 and 2.

12.3.2.1 Subject Disposition

The number and percentage of subjects in each disposition category (e.g., randomized, included in FAS, completing treatment period, completing the Follow-up Telephone Contact, and discontinuing study with a breakdown of the reasons for discontinuation) may be summarized by various categories including treatment sequence and overall.

12.3.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics (e.g., age, sex, race, weight, height, and genotype) will be summarized by treatment sequence and overall.

12.3.2.3 Prior and Concomitant Medications

Medications used in this study will be coded by using the World Health Organization Drug Dictionary Enhanced and will be defined as follows:

- Prior medication: medication taken before initial dosing with study drug, regardless of when it ended.
- Concomitant medication: medication received at or after initial dosing of study drug, or those received before initial dosing with study drug that continued after initial dosing of study drug.

Note that the medication taken before initial dosing of study drug and continued after initial dosing will be summarized as prior medication, and separately as concomitant medication. Handling of missing dates (e.g., missing start/end date) will be discussed in the SAP.

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 in 3 ways:

- exposure during Part 1,
- exposure during Part 2, and
- cumulative ivacaftor exposure (Parts 1 and 2).

Details will be provided in the SAP.

12.3.3 Part 1 Efficacy Analysis

12.3.3.1 Analysis of Primary Variable

The primary efficacy variable is the absolute change from baseline through 8 weeks of treatment in LCI endpoint. The analysis will be based on a mixed-effects model for repeated measures (MMRM) utilizing the FAS.

The model will include the absolute change from study baseline in each period as the dependent variable; sequence, treatment, period, and visit within period as fixed effects; LCI baseline and

age as covariates; and subject nested within sequence as the random effect. Unstructured covariance matrix is further assumed for the repeated measurements of the same subject within each 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 average treatment effect across all post-baseline visits within the treatment period will be obtained from the model. Comparative treatment assessment will be performed using the P value and 95% confidence interval (CI). Carry-over effect will be assessed by the sequence effect in the model.

Because of the low expected power, a Bayesian analysis may be performed. The analysis will compute the posterior probability that the treatment difference is greater than 0, based on a non-informative prior distribution. There are no specific success criteria due to the low subject numbers available for analysis.

Summary and individual listings of efficacy data will be generated. A more detailed description of the planned statistical analysis of efficacy endpoints will be presented in the SAP.

12.3.3.2 Analysis of Secondary Efficacy Variables

The analysis of secondary endpoints as listed in Section 7.1.2, excluding the safety endpoint, will consist of summary statistics only, due to the low number of subjects available for analysis.

No statistical multiplicity adjustment will be made for secondary variables.

[redacted]

12.3.4 Part 2 Efficacy Analysis

Data collected from subjects in Part 2 will be presented in subject listings only. Summary statistics may also be provided.

12.3.5 Safety Analysis

The overall safety profile of ivacaftor versus placebo will be assessed in terms of the following secondary (safety) endpoints:

- Incidence of treatment-emergent AEs (TEAEs)
- Clinical laboratory values (including LFTs)
- OEs

All safety assessments will be conducted across the entire study, regardless of study part.

The incidence of TEAEs is the key safety endpoint and will be summarized by treatment and by means of contingency tables (n, percentage). A TEAE will be defined as any AE that started at or after initial dosing of study drug or increased in severity at or after initial dosing of study drug. For other safety endpoints (e.g., vital signs), the raw values and changes from baseline will be summarized by treatment, as appropriate. Additionally, all subject safety data will be presented in subject data listings. All summaries will be based on the Safety Set (see Section 12.2).

12.3.5.1 Adverse Events

TEAEs, defined as AEs that developed or worsened on or after the first dose of study drug will be summarized. AEs will be attributed to study drug depending on the date of onset of the AE and the treatment that the subject is receiving at the time of onset of the AEs. If a subject discontinued treatment during a specific period, the Safety Follow-up Visit will be considered as the end date. TEAEs will hereafter be referred to as AEs. AE summary tables will include the following:

- All AEs
- Related (defined as possibly related or related) AEs
- AEs leading to study drug treatment discontinuation
- SAEs
- AEs by severity
- AEs by relationship

Summaries will be presented by MedDRA system organ class and preferred term using frequency counts and percentages. A subject with multiple occurrences of the same AE or a continuing AE will be counted only once, with the highest severity or relationship.

In addition, a listing containing individual subject AE data for all deaths and other serious and significant AEs will be provided.

12.3.5.2 Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using SI units. Continuous chemistry, hematology, and coagulation results will be summarized by treatment at each visit. Changes from baseline will also be summarized. The number and percentage of subjects with shift changes from baseline based on the laboratory normal ranges will be tabulated. The maximum on-treatment results will be tabulated by treatment and study part.

Urinalysis results will be listed but not summarized. In addition, a listing containing individual subject hematology, chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

Clinically significant abnormal findings will be reported as AEs.

Summary and analysis of elevation of LFT parameters will be provided in detail in the SAP.

12.3.5.3 Vital Signs

Vital signs will be presented as a data listing; a summary table by treatment sequence will also be provided.

12.3.5.4 Physical Examination

Physical examination findings will be presented as a data listing only. Clinically relevant results identified after screening will be reported as AEs.

12.3.5.5 Other Safety Analysis

Not applicable.

12.3.6 Interim and IDMC Analyses

Following a review of study enrollment and assessment of the available number of potential subjects for this study, Vertex decided to close enrollment as of 21 February 2017 and withdraw subjects in order to terminate the study. As a result, no interim or IDMC analyses will be conducted (See Section 8.1). The IDMC Charter will be updated following approval of the protocol amendment to reflect changes impacted by the decision to terminate the study early.

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 preexisting 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, physical examinations, and vital signs, will be assessed and those deemed as clinically significant worsening from baseline 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 clinical status of the subject indicates a life-threatening AE.

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 Telephone Contact: through the Safety Follow-up Telephone Contact
- 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 Termination of Treatment Visit, if that visit is 3 weeks or later following the last dose of study drug (see Section 8.1.7).

All subjects will be queried, using non-leading 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 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 non-serious AEs. The guidance available at the following website will be consulted: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007, Center for Biologics Evaluation and Research, http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm; (Accessed October 2016). The severity of an AE that does not appear in this scale 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 experience 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 re-appeared 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 should 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) should 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 Telephone Contact and/or Early Termination of Treatment Visit, regardless of causality, will be reported by the investigator to Vertex GPS. In addition, all SAEs that occur after the study has concluded and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours**.

SAEs 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 Clinical Trials 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 Vertex Clinical Trials 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 Vertex Clinical Trial 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 Global Patient Safety via
Email: [redacted] (Preferred Choice)
Or via 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 protocol will be fully documented in the source documentation and in a protocol deviation log.

13.2.4 Access to Records

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

13.2.5 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all CRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers and access to subject names linked to such numbers shall be limited to the site and the study doctor 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 CRFs/SAE forms and the review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/EC, 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.

Following a review of study enrollment and assessment of the available number of potential subjects for this study, Vertex decided to close enrollment and terminate the study. After the protocol amendment has been approved at a site, subjects in Part 1 will be withdrawn from the study at their Week 24 Visit, and subjects in Part 2 will be withdrawn from the study and requested to complete the Early Termination of Treatment Visit (see Section 8.1).

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 a CRF by study site personnel using a secure, validated web-based electronic data capture (EDC) application. Vertex will have read-only access to site-entered clinical data in the EDC application.

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

13.4 Monitoring

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

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

13.5 Electronic Data Capture

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

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

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

The audit trail entry will show the user's identification information and the date and time of any correction. The investigator will provide formal approval of all the information in the CRFs, including any changes made to the CRFs, 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 CD or other electronic media will be placed in the investigator's study file.

14 REFERENCES

1 Cystic Fibrosis Foundation Patient Registry. 2010 Annual Data Report. Bethesda, Maryland. 2011 Cystic Fibrosis Foundation.

2 Farrell PM. The prevalence of cystic fibrosis in the European Union. J Cyst Fibrosis. 2008;7:450-3.

3 O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet. 2009;373:1891-904.

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

5 Sheppard MN, Nicholson AG. The pathology of cystic fibrosis. Current Diagnostic Pathology. 2002;8:50-9.

6 Konstan MW, VanDevanter DR, Rasouliyan L, Pasta DJ, Yegin A, Morgan WJ, et al. Trends in the use of routine therapies in cystic fibrosis: 1995-2005. Pediatr Pulmonol. 2010;45:1167-72.

7 United Kingdom Cystic Fibrosis Registry. 2009 Annual Data Report. London, United Kingdom. 2011 Cystic Fibrosis Trust.

8 Cystic Fibrosis Mutation Database (CFTR1). Cystic Fibrosis Centre at the Hospital for Sick Children in Toronto Web site. Available at: http://www.genet.sickkids.on.ca/cftr/StatisticsPage.html. Accessed 27 October 2016.

9 McKone EF, Goss CH, Aitken ML. *CFTR* genotype as a predictor of prognosis in cystic fibrosis. Chest. 2006;130:1441-7.

10 McKone EF, Emerson SS, Edwards KL, Aitken ML. Effect of genotype on phenotype and mortality in cystic fibrosis: a retrospective cohort study. The Lancet. 2003;361:1671-6.

11 Dalemans W, Barbry P, Champigny G, Jallat S, Dott K, Dreyer D, et al. Altered chloride ion channel kinetics associated with the delta F508 cystic fibrosis mutation. Nature. 1991;354:526-8.

12 Illek B, Zhang L, Lewis NC, Moss RB, Dong JY, Fischer H. Defective function of the cystic fibrosis-causing missense mutation *G551D* is recovered by genistein. Am J Physiol. 1999;277:C833-9.

13 Van Goor F, Hadida S, Grootenhuis P. Pharmacological rescue of mutant CFTR function for the treatment of cystic fibrosis. Top Med Chem. 2008;3:9-120.

14 Verkman AS, Galietta LJ. Chloride channels as drug targets. Nat Rev Drug Discov. 2009;8:153-71.

15 Stick SM, Brennan S, Murray C, Douglas T, von Ungern-Sternberg BS, Garratt LW, et al. Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF). Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening. J Pediatr. 2009;155:623-8.

16 Döring G, Hoiby N, Consensus Study Group. Early intervention and prevention of lung disease in cystic fibrosis: a European consensus. J Cyst Fibros. 2004;3:67-91.

17 Farrell PM, Kosorok MR, Rock MJ, Laxova A, Zeng L, Lai HC, et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. Pediatrics. 2001;107:1-13.

18 Sawicki G, McKone E, Pasta D, Wagener J, Johnson C, Konstan MW. The effect of ivacaftor on the rate of lung function decline in CF patients with a *G551D-CFTR* mutation. J Cyst Fibros. 2014;13 (Suppl 2):S6.

19 Horsley A. Lung clearance index in the assessment of airways disease. Respir Med. 2009;103:793-9.

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

21 Yankaskas JR, Marshall BC, Sufian B, Simon RH, Rodman D. Cystic fibrosis adult care. Chest. 2004;125:1-39.

22 Corey M. Power considerations for studies of lung function in cystic fibrosis. Proc Am Thorac Soc. 2007;4:334-7.

23 Macklem PT. The physiology of small airways. Am J Respir Crit Care Med. 1998;157:S181-3.

24 Tiddens HA. Detecting early structural lung damage in cystic fibrosis. Pediatr Pulmonal. 2002;34:228-31.

25 Owens CM, Aurora P, Stanojevic S, Bush A, Wade A, Oliver C, et al. Lung Clearance Index and HRCT are complementary markers of lung abnormalities in young children with CF. Thorax. 2011;66(6):481-8.

26 Ellemunter H, Fuchs SI, Unsinn KM, Freund MC, Waltner-Romen M, Steinkamp G, et al. Sensitivity of Lung Clearance Index and chest computed tomography in early CF lung disease. Respir Med. 2010;104:1834-42.

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

28 de Jong PA, Ottink MD, Robben SG, Lequin MH, Hop WC, Hendriks JJ, et al. Pulmonary disease assessment in cystic fibrosis: comparison of CT scoring systems and value of bronchial and arterial dimension measurements. Radiology. 2004;231:434-9.

29 Brody AS, Tiddens HA, Castile RG, Coxson HO, de Jong PA, Goldin J, et al. Computed tomography in the evaluation of cystic fibrosis lung disease. Am J Respir Crit Care Med. 2005;172:1246-52.

30 Jensen R, Stanojevic S, Gibney K, Salazar JG, Gustafsson P, Subbarao P, et al. Multiple breath nitrogen washout: a feasible alternative to mass spectrometry. PLoS One. 2013;8(2):e56868. doi:10.1371/journal.pone.0056868.

31 Lum S, Gustafsson P, Ljungberg H, Hülskamp G, Bush A, Carr SB, et al. London Cystic Fibrosis Collaboration. Early detection of cystic fibrosis lung disease: multiple-breath washout versus raised volume tests. Thorax. 2007;62:341-7.

32 Sheikh SI, Long FR, McCoy KS, Johnson T, Ryan-Wenger NA, Hayes D Jr. Computed tomography correlates with improvement in ivacaftor treatment in cystic fibrosis patients with G551D mutation. J Cyst Fibros. 2015;14:84-9.

33 Stanojevic S, Jensen R, Sundaralingam D, Salazar JG, Yammine S, Singer F, et al. Alternative outcomes for the multiple breath washout in children with CF. J Cyst Fibros. 2015. Available from: http://dx.doi.org/10.1016/j.jcf.2014.12.008.

34 Tiddens HA, de Jong PA. Imaging and clinical trials in cystic fibrosis. Proc Am Thorac Soc. 2007;4:343-6.

35 Pencharz PB, Durie PR. Pathogenesis of malnutrition in cystic fibrosis, and its treatment. Clin Nutr. 2000;19:387-94.

36 Sharma R, Florea VG, Bolger AP, Doehner W, Florea ND, Coats AJS, et al. Wasting as an independent predictor of mortality in patients with cystic fibrosis. Thorax. 2001;56:746-50.

37 Konstan MW, Morgan WJ, Butler SM, Pasta DJ, Craib ML, Silva SJ, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. Pediatr Pulmonol. 2007;151:134-9.

38 Sanders DB, Bittner RCL, Rosenfeld M, Redding GJ, Goss CH. Pulmonary exacerbation and subsequent FEV_1 decline in both adults and children with cystic fibrosis. J Pediatr. 2011;46:393-400.

39 Mayer-Hamblett N, Ramsey BW, Kronmal RA. Advancing outcome measures for the new era of drug development in cystic fibrosis. Proc Am Thorac Soc. 2007;4:370-7.

40 Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. N Engl J Med. 1994;331:637-42.

41 Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. N Eng J Med. 1999;340(1):23-30.

42 Rosenfeld M, Emerson J, Williams-Warren J, Pepe M, Smith A, Montgomery AB, et al. Defining a pulmonary exacerbation in cystic fibrosis. J Pediatr. 2001;139:359-65.

43 Rabin HR, Butler SM, Johnson CA, Colin AA, FitzSimmons SC, Geller DE, et al. Pulmonary exacerbations in cystic fibrosis. Pediatr Pulmonol. 2004;37:400-6.

44 Blumer JL, Saiman L, Konstan MW, Melnick D. The efficacy and safety of meropenem and tobramycin vs. ceftazidime and tobramycin in the treatment of acute pulmonary exacerbations in patients with cystic fibrosis. Chest. 2005;128:2336-46.

45 Davis SD, Brody AS, Emond MJ, Brumback LC, Rosenfeld M. Endpoints for clinical trials in young children with cystic fibrosis. Proc Am Thorac Soc. 2007; 4:418-30.

46 Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol. 2001;153(4):345-52.

47 Rosenfeld M. An overview of endpoints for cystic fibrosis clinical trials. Proc Am Thorac Soc. 2007;4(4):299-301.

48 Hayes D Jr, Kraman SS. The physiologic basis of spirometry. Respir Care. 2009;54:1717-26.

49 Borowitz D, Baker SS, Duffy L, Baker RD, Fitzpatrick L, Gyamfi J et al. Use of fecal elastase-1 to classify pancreatic status in patients with cystic fibrosis. J Pedia. 2004;145:322-6.

50 Demko CA, Byard PJ, Davis PB. Gender differences in cystic fibrosis: *Pseudomonas aeruginosa* infection. J Clin Epidemiol. 1995;8:1041-9.

51 Li Z, Kosorok MR, Farrell PM, Laxova A, West SE, Green CG, et al. Longitudinal development of mucoid *Pseudomonas aeruginosa* infection and lung disease progression in children with cystic fibrosis. JAMA. 2005;293:581-8.

52 Kalish LA, Waltz DA, Dovey M, Potter-Bynoe G, McAdam AJ, Lipuma JJ, et al. Impact of *Burkholderia dolosa* on lung function and survival in cystic fibrosis. Am J Respir Crit Care Med. 2006;15:173:421-5.

53 West SE, Zeng L, Lee BL, Kosorok MR, Laxova A, Rock MJ, et al. Respiratory infections with *Pseudomonas aeruginosa* in children with cystic fibrosis: early detection by serology and assessment of risk factors. JAMA. 2002;12:287(22):2958-67.

54 Weintraub A, Blau H, Mussaffi H, Picard E, Bentur L, Kerem E, et al. Exocrine pancreatic function testing in patients with cystic fibrosis and pancreatic sufficiency: a correlation study, J Pediatr Gatroenterol Nutr. 2009;48:306-10.

55 Bruzzese E, Raia V, Gaudiello G, Polito G, Buccigrossi V, Formicola V, et al. Intestinal inflammation is a frequent feature of cystic fibrosis and is reduced by probiotic administration. Aliment Pharmacol Ther. 2004;20:813-9.

56 Baltieri S, Pinali L, Bortoluzzi C, Volpi S, Tridello G, Tiddens HA, et al. Evaluation of lung disease progression with CT Brody score in patients with cystic fibrosis. 2014;doi: 10.1594/ecr2014/C-1098.

57 Brody AS, Klein JS, Molina PL, Quan J, Bean JA, Wilmott RW. High-resolution computed tomography in young patients with cystic fibrosis: distribution of abnormalities and correlation with pulmonary function tests. J Pediatr. 2004;145:32-8.

58 Loeve M, Gerbrands K, Hop WC, Rosenfeld M, Hartmann IC, Tiddens HA. Bronchiectasis and pulmonary exacerbations in children and young adults with cystic fibrosis. Chest. 2011;140:178-85.

59 Robinson TE, Leung AN, Chen X, Moss RB, Emond MJ. Cystic fibrosis HRCT scores correlate strongly with Pseudomonas infection. Pediatr Pulmonol. 2009;44:1107-7.

60 Rosenow T, Oudraad MCJ, Murray CP, Turkovic L, Kuo W, de Bruijne M, et al. PRAGMA-CF: a quantitative structural lung disease CT outcome in young children with cystic fibrosis. Am J Respir Crit Care Med. 2015;doi: 10.1164/rccm.201501-0061OC.

61 Saiman L, Anstead M, Mayer-Hamblett N, Lands LC, Kloster M, Hocevar-Trnka J, et al. Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with *Pseudomonas aeruginosa*: a randomized controlled trial. JAMA. 2010;303:1707-15.

62 American Thoracic Society. Standardization of spirometry: 1994 update. Am J Respir Crit Care Med. 1995;152:1107-36.

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX15-770-123	Version #: 4.0	Version Date 12 April 2017
Study Title: A Phase 3b, 2-part, Randomized, Double-blind, Placebo-controlled Crossover Study With a Long-term Open-label Period to Investigate Ivacaftor in Subjects With Cystic Fibrosis Aged 3 Through 5 Years Who Have a Specified *CFTR* Gating Mutation		

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

[redacted]

15.2 Investigator Signature Page

Protocol #: VX15-770-123	Version #: 4.0	Version Date 12 April 2017
Study Title: A Phase 3b, 2-part, Randomized, Double-blind, Placebo-controlled Crossover Study With a Long-term Open-label Period to Investigate Ivacaftor in Subjects With Cystic Fibrosis Aged 3 Through 5 Years Who Have a Specified *CFTR* Gating Mutation		

I have read Protocol VX15-770-123, Version 4.0 and agree to conduct the study according to its terms. I understand that all information concerning ivacaftor and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date