1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 2a, Randomized, Double-blind, Placebo-controlled, Incomplete Block, Crossover Study to Evaluate the Safety and Efficacy of VX-371 in Subjects Aged 12 Years or Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation, and Being Treated With Orkambi

Vertex Study Number: VX15-371-101

[redacted]

EudraCT Number: 2015-004841-13

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2 PROTOCOL SYNOPSIS

Title A Phase 2a, Randomized, Double-blind, Placebo-controlled, Incomplete Block, Crossover Study to Evaluate the Safety and Efficacy of VX-371 in Subjects Aged 12 Years or Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation, and Being Treated With Orkambi

Brief Title A Study to Evaluate the Efficacy and Safety of VX-371 in Subjects With Cystic Fibrosis Who Are Homozygous for the *F508del-CFTR* Mutation

Clinical Phase and Clinical Study Type Phase 2a, safety and efficacy

Objectives

Primary

To evaluate the safety and efficacy of treatment with VX-371 in hypertonic saline (HS) compared to HS alone in subjects with cystic fibrosis (CF) who are ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi

Secondary

- To evaluate the efficacy of treatment with VX-371 in HS compared with placebo in subjects with CF who are ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi
- To evaluate the efficacy of treatment with VX-371 in HS compared with VX-371 in placebo in subjects with CF who are ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi
- To evaluate the efficacy of treatment with VX-371 in placebo compared with placebo in subjects with CF who are ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi
- To investigate the pharmacokinetics (PK) of VX-371 in subjects with CF who are ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi

Endpoints

Primary

- Results of safety and tolerability assessments of adverse events, spirometry, clinical laboratory values (urine, serum, and plasma chemistry, hematology, and coagulation studies), standard 12-lead electrocardiograms (ECGs), vital signs, and ophthalmologic examinations
- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline at Day 28 in each Treatment Period

Secondary

PK parameters for VX-371

[redacted]

Number of Subjects Approximately 150 subjects will be randomized to 1 of 4 treatment sequences

Study Population

Male and female subjects aged 12 years or older with CF who are homozygous for the *F508del-CFTR* mutation and being treated with Orkambi

Investigational Drug

Active substance: VX-371

Activity: Epithelial sodium channel (ENaC) inhibitor

Strength and Route of Administration: 85 µg VX-371 in 3 mL 0.17% saline (placebo), oral nebulized inhalation

Active substance: VX-371 + HS

Activity: ENaC inhibitor

Strength and Route of Administration: 85 µg VX-371 + 3 mL 4.2% HS, oral nebulized inhalation

Active substance: HS

Activity: Osmolyte

Strength and Route of Administration: 3 mL 4.2% HS, oral nebulized inhalation

Active substance: Not applicable

Activity: placebo

Strength and Route of Administration: 3 mL 0.17% saline, oral nebulized inhalation

Active substance: lumacaftor and ivacaftor (fixed-dose combination with lumacaftor and ivacaftor)

Activity: CFTR corrector and potentiator (chloride ion [Cl^-] secretion)

Strength and Route of Administration: lumacaftor 200-mg/ivacaftor 125-mg tablets for oral administration

Study Duration

Excluding the Screening Period, the planned study duration is up to 115 days for Orkambi+/HS- subjects and up to 143 days for Orkambi-/HS-, Orkambi-/HS+, and Orkambi+/HS+ subjects.

Study Design

Phase 2a, randomized, double-blind, placebo-controlled, incomplete block, crossover, multicenter, study in subjects ≥12 years of age with CF who are homozygous for the *F508del-CFTR* mutation and who are being treated with Orkambi.

Subjects will be randomized to 1 of 4 treatment sequences that will each be composed of: Treatment Period 1 → Washout → Treatment Period 2.

This study includes the following:

- Screening Period:
- Day -28 to Day -1 for Orkambi+/HS- subjects
- Day -56 to Day -29 for Orkambi-/HS-, Orkambi-/HS+, and Orkambi+/HS+ subjects
- Run-in Period: Day -28 to Day -1 for Orkambi-/HS-, Orkambi-/HS+, and Orkambi+/HS+ subjects
- Treatment Period 1 through Treatment Period 2:
  - Treatment Period 1: Day 1 (first dose of inhaled study drug) through Day 28
  - Washout Period: Day 29 through Day 56
  - Treatment Period 2: Day 57 through Day 84
- Early Termination of Treatment Visit for a subject who discontinues from study

drug treatment(s) but who does not complete the remaining assessments in the treatment period during which study drug treatment(s) is discontinued.

- Safety Follow-up Telephone Contact: 28 days (+ 3 days) after the Day 84 Visit; or 28 days (+ 3 days) after the Day 28 Visit for a subject who completes this visit but who will not be continuing into Treatment Period 2 (Note: Under certain circumstances, a safety Follow-up Telephone Contact may not be appropriate, and a Safety Follow-up Visit may be required.)
- A Safety Follow-up Visit will occur 28 days (+ 3 days) after a subject's last dose of study drug (whether inhaled study drug or lumacaftor/ivacaftor) in subjects who:
  - prematurely discontinue one or both study drugs during the course of either treatment period and do not complete the remaining assessments in the treatment period in which discontinuation occurred. In this circumstance, an ETT Visit is required in addition to the Safety Follow-up Visit (see Section 8.1.4).
  - have a clinical finding during the treatment period or during the 28-day Safety Follow-up Period that requires follow-up in the estimation of the PI. An ETT Visit may or may not be required in this circumstance (see Section 8.1.4).

Assessments

Efficacy: spirometry, [redacted]

Safety: adverse events, spirometry, clinical laboratory values (urine, serum and plasma chemistry, hematology, and coagulation studies), ECGs, physical examinations, vital signs, and ophthalmologic examinations (for subjects <18 years of age at Screening only)

PK: VX-371, [redacted]

Statistical Analyses

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

The primary efficacy objective of this study is to evaluate the efficacy of treatment with VX-371 in HS compared to HS. For efficacy analysis, the statistical inference will be based on change from study baseline. The null hypothesis to be tested is that the mean change from study baseline in $ppFEV_1$ to the Day 28 measurements is the same for VX-371 in combination with HS versus HS alone.

To have a feasible sample size and study duration, this study uses a crossover design. Assuming a standard deviation (SD) of 7 percentage points, 50 subjects per sequence are needed to have an approximately 81% power to detect a 3 percentage point treatment difference in the mean absolute change in $ppFEV_1$ from study baseline at Day 28 between VX-371 + HS and HS alone. The study will have approximately 80% power to detect a 3 percentage point (within treatment) change from baseline at Day 28 in $ppFEV_1$ for VX-371. A 2-sided significance level of 0.05 was used in the sample size calculations. The sample size also takes into consideration an assumed dropout rate of 10%.

The primary efficacy endpoint is the absolute change in $ppFEV_1$ from study baseline at Day 28 in each Treatment Period. The primary efficacy analysis is based on a mixed-effects model. This model will include the absolute change from study baseline in $ppFEV_1$ at Day 28 as the dependent variable, study baseline for $ppFEV_1$, treatment, and period as fixed effects, and subject nested within sequence as a random effect. The within-subject covariance will be assumed to have the compound symmetry structure. Denominator degrees of freedom for the F-test for fixed effects will be estimated using the Kenward-Roger approximation. No imputation of missing

data will be done. Assuming that the subjects have dropped out at random, an estimate of treatment effect will be based on such subjects and will then be combined with the estimate from subjects who have data in both treatment periods with weights based on the precision of these estimates.

The estimated mean of the dependent variable, a 95% CI, and a 2-sided *P* value will be provided for each treatment. Similarly, the estimated between-treatment differences along with the corresponding 95% CI and 2-sided *P* values will be presented. Additionally, a mixed model of repeated measures (MMRM) will be used with period, study baseline for $ppFEV_1$, visit, treatment, and treatment by visit, study baseline for $ppFEV_1$ by visit, as fixed effects and subject nested within sequence as a random effect. The absolute change from study baseline in $ppFEV_1$ will be the dependent variable. The repeated measures analysis will enable use of all post-baseline available data and provide least square means estimates at each visit within a given treatment as well as estimates of treatment difference at each visit or across all visits. [redacted]

IDMC Reviews The independent data monitoring committee (IDMC) will conduct regular planned safety reviews of study data as outlined in the IDMC charter.

3 SCHEDULE OF ASSESSMENTS

Schedules of Assessments are shown in Table 3-1, Table 3-2, Table 3-3, and Table 3-4.

During the Screening Visit it should be determined whether the subject will have a Run-in Period. Table 8-2 outlines the assignment of subjects to a Run-in Period.

Table 3-1 Study VX15-371-101: Screening Period for All Subjects

Event/Assessment	Screening Period (Day-28 to Day -1 for Orkambi+/HS- Subjects or Day -56 to Day -29 for Orkambi-/HS+, Orkambi-/HS-, and Orkambi+/HS+ Subjects[a])
Clinic visit	X
Informed consent/assent	X
Inclusion/exclusion criteria review	X
Demography	X
Medical history	X
Ophthalmologic history	X
Medications review	X
Height and weight[b]	X
Vital signs	X
Ophthalmologic examination (only for pediatric subjects <18 years of age)	X
Physical examination[c]	X

[a] All Screening assessments must be completed before the Day 1 Visit for Orkambi+/HS- subjects and before the Day -28 Visit for Orkambi-/HS+, Orkambi-/HS-, and Orkambi+/HS+ subjects. Subjects may be rescreened after discussion with, and approval from, the medical monitor (see Section 8.1.1.2).

[b] Height and weight will be measured with shoes off.

[c] A full physical examination will be performed at the Screening Visit (see Section 11.6.3).

Table 3-1 Study VX15-371-101: Screening Period for All Subjects

Event/Assessment	Screening Period (Day-28 to Day -1 for Orkambi+/HS- Subjects or Day -56 to Day -29 for Orkambi-/HS+, Orkambi-/HS-, and Orkambi+/HS+ Subjects[a])
Standard 12-lead ECG[d]	X
Sweat chloride[e]	X
CFTR genotype[f]	X
Serum β-hCG[g]	X
Serum FSH[h]	X
Urine tests	X
Serum and plasma chemistry	X
Hematology	X
Coagulation	X
Spirometry	X
Lumacaftor/ivacaftor dosing[i]	lumacaftor 400 mg/ivacaftor 250 mg q12h
[redacted]	
AEs and SAEs	Continuous, from signing of ICF (and assent form, if applicable) through Safety Follow-up Telephone Contact

[d] A standard 12-lead ECG will be performed after the subject has been seated or supine for at least 5 minutes (Section 11.6.4).

[e] A sweat chloride test must be performed at the Screening Visit if an eligible sweat chloride value is not available in the subject's medical records and the Screening Visit value is needed to establish eligibility. For subjects using sweat chloride values documented in their medical records to establish eligibility, the sweat chloride test at the Screening Visit is optional. Collection of sweat chloride will not overlap with any other study assessments.

[f] *CFTR* genotyping will be performed to confirm that the subject is homozygous for the *F508del-CFTR* mutation and the 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. *Note: Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study*.

[g] A pregnancy test will be performed for all female subjects of childbearing potential.

[h] Follicle-stimulating hormone (FSH) will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be ≥40 mIU/mL to be considered postmenopausal.

[i] Subjects are to take 2 tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) orally q12h with fat-containing food (Section 10.2.2).

Table 3-2 Study VX15-371-101: Run-in Period for Orkambi-/HS-, Orkambi-/HS+, and Orkambi+/HS+ Subjects

	Run-in Period[a] (Day -28 to Day -1)	
Event/Assessment	**Day -28 (± 2 days)**	**Day -14 (± 2 days)**
Clinic visit	X	X
Vital signs	X	X
Physical examination[b]	X	X
Meal or snack at study center[c]	X	X
Lumacaftor/ivacaftor dosing[d]	lumacaftor 400 mg/ivacaftor 250 mg q12h	
[redacted]		
Adverse events and serious adverse events	Continuous, from signing of ICF (and assent form, if applicable) through Safety Follow-up Telephone Contact	

[a] During the Run-in Period, all subjects who are receiving HS as part of their CF standard of care will washout from HS for 28 days before dosing with study drug and will remain off HS through the Safety Follow-up Telephone Contact.

[b] An abbreviated physical examination will be performed at the Day -28 and Day -14 Visits (see Section 11.6.3).

[c] At the scheduled visits indicated, if the subject has not taken the morning dose of lumacaftor/ivacaftor before coming to the study visit, a fat-containing meal or snack will be provided with that dose.

[d] Subjects are to take 2 tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) orally q12h with fat-containing food (Section 10.2.2).

Table 3-3 Study VX15-371-101: Treatment Period

	Treatment Period[a]								
	Treatment Period 1 (Day 1 to Day 28)				Washout[b] (Day 29 to Day 56) (+ 3 days)	Treatment Period 2 (Day 57 to Day 84)			
Event/Assessment	**Day 1**	**Day 3 (± 1 day)**	**Day 14 (± 3 days)**	**Day 28 (- 2 days)**		**Day 57**	**Day 59 (± 1 day)**	**Day 70 (± 3 days)**	**Day 84 (- 2 days)**
Clinic visit	X		X	X		X		X	X
Telephone contact[c]		X					X		
Inclusion/exclusion criteria review	X								
Randomization[d]	X								
[redacted]									
Height and weight[f]	X			X		X			X
Vital signs[g]	X		X	X		X		X	X
Physical examination[h]	X			X		X			X
Standard 12-lead ECG[i]	X		X	X		X		X	X

[a] See Section 8.1.4 for guidance about discontinuation of study drug treatment.

[b] The Washout Period may be for acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) upon discussion with and approval by the medical monitor (see Section 8.1.3.2).

[c] A telephone contact will occur on Day 3 and Day 59 of the study for safety purposes (e.g., inquiry about adverse events).

[d] 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. *Note: 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*.

[redacted]

[f] Height and weight will be measured with shoes off.

[g] All vital signs will be collected within 60 minutes before inhaled study drug dosing. Only pulse rate and blood pressure will be collected 90 (± 30) minutes after inhaled study drug dosing. Vital signs will be assessed after the subject has been seated or supine for at least 5 minutes (Section 11.6.3).

[h] An abbreviated physical examination will be performed before dosing with inhaled study drug (see Section 11.6.3).

[i] The ECG will be performed 60 (± 30) minutes after completion of inhaled study drug dosing and after the subject has been seated or supine for at least 5 minutes (Section 11.6.4).

Table 3-3 Study VX15-371-101: Treatment Period

	Treatment Period[a]							
	Treatment Period 1 (Day 1 to Day 28)				Washout[b] (Day 29 to Day 56) (+ 3 days)	Treatment Period 2 (Day 57 to Day 84)		
Event/Assessment	**Day 1**	**Day 3 (± 1 day)**	**Day 14 (± 3 days)**	**Day 28 (- 2 days)**		**Day 57**	**Day 59 (± 1 day)**	**Day 70 (± 3 days)**	**Day 84 (- 2 days)**
[redacted]									
Spirometry[k]	X		X	X		X		X	X
Urine pregnancy test[l]	X			X		X			X
Urine tests[m]	X		X	X		X		X	X
[redacted]									
Serum and plasma chemistry[o]	X		X	X		X		X	X
Hematology	X			X		X			X
Coagulation	X			X		X			X

[redacted]

k The spirometry assessment will be performed within 60 (± 10) minutes before and 30 (± 5) minutes) after the dose of inhaled study drug is administered.

l Pregnancy tests will only be administered to female subjects of childbearing potential (see Section 11.6.2).

m On Day 1 and Day 57, a urine sample will be collected 90 (+ 5) minutes before dosing with inhaled study drug. A urine sample will also be collected at 90 (± 60) minutes after completion of dosing with inhaled study drug at the Day 14, Day 28, Day 70, and Day 84 Visits.

[redacted]

o Subjects with a potassium level that is ≤0.4 units below the ULN at the Day 1 or Day 57 Visit will be required to have a blood sample collected for a repeat evaluation of plasma potassium within 7 (± 2) days (see Section 11.6.2.2).

Table 3-3 Study VX15-371-101: Treatment Period

	Treatment Period[a]							
	Treatment Period 1 (Day 1 to Day 28)				Washout[b] (Day 29 to Day 56) (+ 3 days)	Treatment Period 2 (Day 57 to Day 84)		
Event/Assessment	**Day 1**	**Day 3 (± 1 day)**	**Day 14 (± 3 days)**	**Day 28 (- 2 days)**		**Day 57**	**Day 59 (± 1 day)**	**Day 70 (± 3 days)**	**Day 84 (- 2 days)**
Urine for PK analysis[p]	X		X	X		X		X	X
Blood for PK analysis[q]	X		X	X		X		X	X
Meal or snack at study center[r]	X		X	X		X		X	X
Inhaled study drug dosing[s]	X		X	**X**[t]		X		X	**X**[t]
Lumacaftor/ivacaftor dosing[u]				lumacaftor 400 mg/ivacaftor 250 mg q12h					
Inhaled study drug count	X		X	X		X		X	X
Lumacaftor/ivacaftor drug count	X		X	X		X		X	X

[p] A urine sample for evaluation of VX-371 will be collected within 90 (+ 5) minutes before and 90 (± 60) minutes after completion of dosing with inhaled study drug at the Day 1, Day 14, Day 28, Day 57, Day 70, and Day 84 Visits (see Section 11.3.2).

[q] Blood samples for the PK assessment will be analyzed for VX-371 [redacted]. For the evaluation of VX-371, a blood sample will be collected within 90 (+ 5) minutes before dosing with inhaled study drug and at 60 (± 30) minutes after completion of inhaled study drug dosing at the Day 1, Day 14, Day 28, Day 57, Day 70, and Day 84 Visits. [redacted]

[r] At the scheduled visits indicated, if the subject has not taken the morning dose of lumacaftor/ivacaftor before coming to the study visit, a meal or snack will be provided with that dose after all predose assessments have occurred.

[s] Inhaled study drug will be administered from Day 1 to Day 28 and from Day 57 to Day 84. Inhaled study drug should be administered by nebulization twice daily (bid) approximately 10 to 12 hours apart for oral inhalation (see Section 10.2.1). Inhaled study drug will be administered at the clinic at the Day 1, Day 14, Day 28, Day 57, Day 70, and Day 84 Visits.

[t] The last dose of inhaled study drug in Treatment Period 1 and Treatment Period 2 is the dose of study drug received at the Day 28 and Day 84 Visits, respectively.

[u] Subjects are to take 2 tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) orally q12h with fat-containing food (Section 10.2.2). The last dose of Orkambi during the Run-in Period will be the morning dose of the Day 1 Visit (Section 8.1.2).

Table 3-3 Study VX15-371-101: Treatment Period

	Treatment Period[a]							
	Treatment Period 1 (Day 1 to Day 28)				Washout[b] (Day 29 to Day 56) (+ 3 days)	Treatment Period 2 (Day 57 to Day 84)		
Event/Assessment	**Day 1**	**Day 3 (± 1 day)**	**Day 14 (± 3 days)**	**Day 28 (- 2 days)**		**Day 57**	**Day 59 (± 1 day)**	**Day 70 (± 3 days)**	**Day 84 (- 2 days)**
Dispense nebulizer and/or nebulizer handset[v]	X					X			
Collect nebulizer and/or nebulizer handset[w]				X					X
Medications review	X		X	X		X		X	X
Concomitant treatments and procedures	X		X	X		X		X	X
[redacted]									
Adverse events and serious adverse events	Continuous, from signing of ICF (and assent form, if applicable) through Safety Follow-up Telephone Contact								

[v] A nebulizer device (nebulizer and handset) will be dispensed at the Day 1 Visit. At the Day 57 Visit, a new nebulizer handset will be provided for replacement.

[w] The nebulizer handset used during Treatment Period 1 will be collected at the Day 28 Visit. At the Day 84 Visit, the nebulizer device (nebulizer and handset used during Treatment Period 2) will be collected.

Table 3-4 Study VX15-371-101: Early Termination of Treatment Visit, Safety Follow-up Visit, and Safety Follow-up Telephone Contact

Event/Assessment	Early Termination of Treatment Visit[a]	Safety Follow-up Visit 28 days (+ 3 days) After Last Dose of Study Drug[b]	Safety Follow-up Telephone Contact 28 days (+ 3 days) After the Day 28 or Day 84 Visit[c]
Clinic visit	X	X	
Telephone contact			X
Height and weight[d]	X	X	
Vital signs	X	X	
Physical examination	X	X	
Ophthalmologic examinations[e]	X	X	X
Standard 12-lead ECG[f]	X	X	
Urine pregnancy test[g]	X	X	
Hematology	X	X	
Coagulation	X	X	
Urine tests	X	X	
Serum and plasma chemistry	X	X	
Urine for PK analysis[h]	X		
Blood for PK analysis[i]	X		
Spirometry	X	X	
[redacted]			
Inhaled study drug count	X		
Lumacaftor/ivacaftor drug count	X	X	
Collect nebulizer and nebulizer handset	X		
Concomitant medications	X	X	
Concomitant treatments and procedures	X	X	

[a] See Section 8.1.4 for guidance about discontinuation of study drug treatment.
[b] See Section 8.1.6.
[c] See Section 8.1.5.
[d] Height and weight will be measured with shoes off.
[e] Pediatric subjects <18 years of age at the Screening Visit who discontinue study drug treatment will have an ophthalmologic examination that is to occur between their last dose of study drug and completion of either the ETT Visit or the Safety Follow-up Visit. Pediatric subjects who complete the Day 84 Visit will have an ophthalmologic examination that is to occur between the Day 84 Visit and the Safety Follow-up Telephone Contact. See Section 11.6.5.
[f] The ECG will be performed after the subject has been seated or supine for at least 5 minutes (Section 11.6.4).
[g] Pregnancy tests will only be administered to female subjects of childbearing potential (see Section 11.6.2).
[h] At the ETT Visit, a single urine sample for PK will be collected.
[i] At the ETT Visit, 2 blood samples for PK will be collected, 1 for the evaluation of VX-371 [redacted].

Table 3-4 Study VX15-371-101: Early Termination of Treatment Visit, Safety Follow-up Visit, and Safety Follow-up Telephone Contact

Event/Assessment	Early Termination of Treatment Visit[a]	Safety Follow-up Visit 28 days (+ 3 days) After Last Dose of Study Drug[b]	Safety Follow-up Telephone Contact 28 days (+ 3 days) After the Day 28 or Day 84 Visit[c]
[redacted]			
Adverse events and serious adverse events	Continuous, from signing of ICF (and assent form, if applicable) through Safety Follow-up Telephone Contact		

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Glossary of Terms

Term	Definition
[redacted]	[redacted]
HS-	Subject is not being treated with hypertonic saline (HS) at Screening.
HS+	Subject is being treated with HS at Screening.
Inhaled study drug	VX-371 + placebo, VX-371 + HS, HS, and placebo administered by nebulizer
Orkambi® (lumacaftor/ivacaftor)	Lumacaftor/ivacaftor is the same drug as commercially available Orkambi. These terms are used interchangeably throughout the document.
Orkambi-	Subject is not being treated with Orkambi at Screening.
Orkambi+	Subject is being treated with Orkambi at Screening.
P-1037	VX-371 has been developed under the name P-1037 by Parion Sciences Incorporated.
Study drug	Unless otherwise specified, the term “study drug” includes both inhaled study drug and orally administered lumacaftor/ivacaftor.

5 INTRODUCTION

5.1 Background

Cystic fibrosis (CF) affects an estimated 70,000 children and adults worldwide[1] and is the most common fatal genetic disease in persons of European descent.[2] Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is in the mid-40s.[2,3] Although the disease affects multiple organs, most morbidity and mortality is caused by progressive loss of lung function.[4]

CF is an autosomal recessive genetic disease caused by a defect in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), an epithelial chloride ion (Cl^-) channel activated by cyclic AMP-dependent protein kinase A that is responsible for aiding in the regulation of salt and water absorption and secretion in various tissues.[2] This function is defective in patients with CF due to a loss of either cell surface expression and/or function.

More than 1900 mutations in the *CFTR* gene have been identified.[5] The most prevalent mutation is an in-frame deletion in the *CFTR* gene resulting in a loss of phenylalanine at position 508 in the CFTR protein (F508del-CFTR).[5] In the US, almost 87% of patients with CF have at least 1 copy of the *F508del-CFTR* mutation, and approximately 47% have 2 copies.[6] The *F508del-CFTR* mutation interferes with the ability of the CFTR protein to reach and remain at the cell surface, as well as to open and close, resulting in decreased Cl^- transport.[7,8] The combined effect is a marked reduction in F508del-CFTR-mediated Cl^- secretion that impairs fluid regulation and promotes accumulation of thick sticky mucus in the airway. The mucus build-up obstructs the airways and predisposes the patient to chronic lung infections.[9]

Mucociliary clearance (MCC) is an important airway defense mechanism that is essential for respiratory health. The primary function of MCC is to clear inhaled particles, including inflammatory and infectious agents, from the surface of the lung.[10] MCC depends on the coordinated, high frequency beating action of the cilia that cover the inner surface of the airways. Efficient ciliary motion is in turn dependent on proper regulation of hydration on the epithelial surface. Volume depletion of the airway surface liquid (ASL) compromises the efficiency of MCC.[11] Inhaled therapies available to improve MCC include Pulmozyme® (recombinant human dornase alfa, Roche/Genentech), which facilitates expectoration by breaking down DNA and decreasing sputum viscosity, and hypertonic saline (HS), which may improve airway surface hydration and improve MCC.

Despite the availability of the above mentioned therapies to improve MCC, patients with CF experience progressive loss of lung function over time and remain at risk for suffering acute pulmonary exacerbations due to chronic bacterial airway infection, requiring hospitalization and/or treatment with antibiotics. Therefore, additional therapies to improve MCC are needed.

For reasons that are not fully understood, CF is also associated with a paradoxically increased activity of epithelial sodium channels (ENaC). The resulting combination of inadequate secretion of chloride ions and excessive intracellular transport of sodium ions creates an osmotic gradient that results in relative dehydration of the secretions in the airway lumen.[12,13] Inadequate clearance of secretions predisposes the airways to bacterial infection. Recurrent episodes of infection lead to a repetitive cycle of increasing inflammation, airway injury, mucociliary

impairment, hypersecretion, and chronic infection of the airway with mucoid strains of *Pseudomonas aeruginosa*.

When applied topically to the airway, ENaC inhibitors such as amiloride can decrease ENaC activity, increase ASL height, and increase MCC.[14] While amiloride's low potency, hyperkalemia, and short half-life in the airway make it impractical as a clinical therapy, newer generations of inhaled ENaC inhibitors featuring an amiloride pharmacophore have been designed to potently inhibit ENaC function directly on the respiratory epithelium, while minimizing exposure to renal ENaC, thereby reducing the risk of hyperkalemia and increasing the therapeutic index.

5.2 VX-371 Solution for Inhalation

VX-371 is a new chemical entity belonging to a family of amiloride derivatives referred to as pyrazinoylguanidines. VX-371 is a novel ENaC inhibitor that inhibits transport of sodium through direct exofacial block of the ENaC. ENaC is expressed in the apical membrane of epithelial cells lining the respiratory tract, distal nephron, colon, and other organs.[15] Sodium ions enter cells through apical ENaC and are transported out by the Na^+/ K^+ ATPase located at the basolateral membrane.[16,17] In the lungs, ENaC is one of the primary proteins that control the ASL volume and is therefore linked to airway hydration and mucus clearance.[18] Optimal MCC requires that airway secretions be adequately hydrated. ENaC is activated by proteolytic cleavage, which can be due to constitutive proteases such as prostasin or by soluble inflammatory proteases such as neutrophil elastase. Free neutrophil elastase activity is detectable in the sputum of patients with CF and chronic obstructive pulmonary disease (COPD), especially during acute exacerbations. The combination of water loss from the ASL due to ENaC over activity and the increase in mucus production by submucosal glands and goblet cells means that the solid fraction of airway secretions in CF exceeds the threshold required for optimal MCC. It is hypothesized that the inhibition of ENaC activity with VX-371 will increase hydration of airway secretions rendering them more susceptible to MCC and cough clearance in subjects with CF.

[redacted] and later by Parion Sciences Incorporated (Parion) where it was known as P-1037. [redacted] P-1037 is the same drug as VX-371.

Additional information is available in the VX-371 Investigator's Brochure.

5.3 Completed and Ongoing Clinical Studies With VX-371

[redacted]

[redacted]

5.3.2 Phase 2a Study with VX-371

Parion is conducting a Phase 2a study (Parion Study G201) with P-1037 (VX-371) in subjects with CF. The goal of Study G201 is to evaluate the safety and efficacy of VX-371 with and without 4.2% HS. The study plans to enroll 150 subjects with CF.

The 2 major differences between the Parion Phase 2a study and the present study are:

- The Parion study is enrolling subjects with CF with no genotype restriction; the present study will enroll only subjects with CF who are homozygous for *F508del-CFTR*.
- The Parion study excludes subjects being treated with any ivacaftor-containing regimen, which includes Orkambi, whereas the present study requires subjects to be treated with Orkambi throughout the study (see Section 5.4 for the rationale behind this requirement).

5.4 Rationale for Present Study

The present study is designed to evaluate the safety and efficacy of VX-371 formulated with 4.2% HS in comparison to 4.2% HS alone on lung function over 28 days of treatment in subjects with CF who are 12 years of age and older who are homozygous for the *F508del-CFTR* mutation. The treatment effect will be evaluated on top of the expected CF standard of treatment for this population, which includes lumacaftor and ivacaftor combination therapy (Orkambi), an FDA-approved treatment for CF in patients homozygous for the *F508del-CFTR* mutation.

Throughout this protocol, the term "inhaled study drug" is used to refer to VX-371 + placebo, VX-371 + HS, HS, and placebo administered by nebulizer. The term "study drug," when it appears without a qualifier, is used to refer to both inhaled study drug and orally administered lumacaftor/ivacaftor. Lumacaftor/ivacaftor is the same drug as commercially available Orkambi, and these terms are used interchangeably.

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the safety and efficacy of treatment with VX-371 in HS compared to HS alone in subjects with CF who are ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi

6.2 Secondary Objectives

- To evaluate the efficacy of treatment with VX-371 in HS compared with placebo in subjects with CF who are ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi
- To evaluate the efficacy of treatment with VX-371 in HS compared with VX-371 in placebo in subjects with CF who are ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi

- To evaluate the efficacy of treatment with VX-371 in placebo compared with placebo in subjects with CF who are ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi
- To investigate the pharmacokinetics (PK) of VX-371 in subjects with CF who are ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi

7 STUDY ENDPOINTS

7.1 Primary Endpoints

- Results of safety and tolerability assessments of adverse events (AEs), spirometry, clinical laboratory values (urine, serum and plasma chemistry, hematology, and coagulation studies), standard 12-lead electrocardiograms (ECGs), vital signs, and ophthalmologic examinations
- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from study baseline at Day 28 in each Treatment Period

7.2 Secondary Endpoint

- PK parameters for VX-371

[redacted]

8 STUDY DESIGN

8.1 Overview of Study Design

This is a Phase 2a, randomized, double-blind, placebo-controlled, incomplete block, crossover, multicenter, study in subjects ≥12 years of age with CF who are homozygous for the *F508del-CFTR* mutation and who are being treated with Orkambi. All subjects must be receiving stable treatment with Orkambi before the first dose of inhaled study drug and through the Safety Follow-up Telephone Contact or Safety Follow-up Visit.

Approximately 150 subjects will be randomized to 1 of the 4 treatment sequences as described in Table 8-1. Each treatment sequence will comprise:

Treatment Period 1 → Washout → Treatment Period 2

Table 8-1 Study VX15-371-101 Treatment Sequences

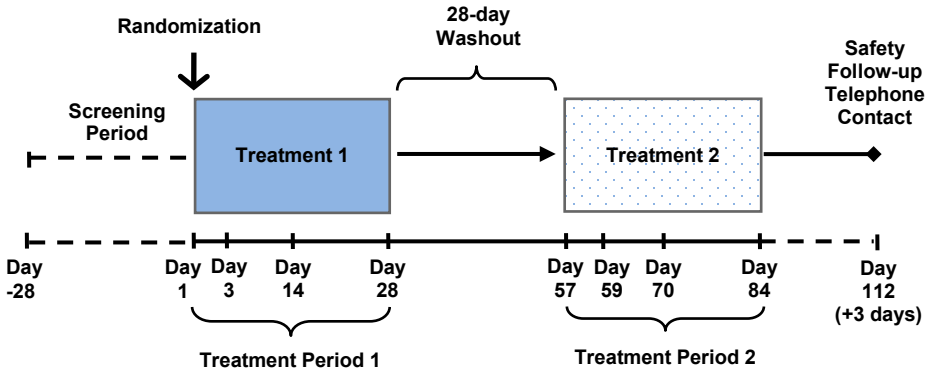
Sequence	Treatment Period 1	Treatment Period 2	N
1	VX-371 + 4.2% HS	4.2% HS	50
2	4.2% HS	VX-371 + 4.2% HS	50
3	VX-371 + 0.17% saline (placebo)	Placebo (0.17% saline)	25
4	Placebo (0.17% saline)	VX-371 + 0.17% saline (placebo)	25

A schematic of the study design is provided in Figure 8-1.

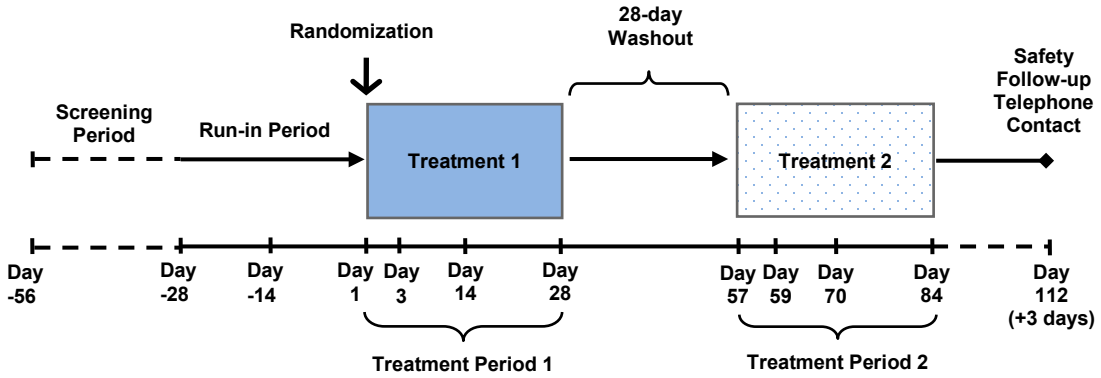
The sponsor may decide to stop enrollment in the 2 treatment sequences containing VX-371 + placebo and placebo for administrative reasons (for example, unexpected difficulty with enrollment). Enrollment would continue in the 2 treatment sequences containing VX-371 + HS and HS to ensure adequate enrollment to maintain statistical power in the 2 treatment sequences yielding data for the study's primary analysis. All planned analyses will be conducted regardless of number of subjects enrolled.

Figure 8-1 Schematic of Study Design VX15-371-101

A. For Orkambi+/HS- Subjects



B. For Orkambi-/HS-, Orkambi-/HS+, and Orkambi+/HS+ Subjects



This study includes the following periods:

- Screening Period:
  - Day -28 to Day -1 relative to the first dose of inhaled study drug for Orkambi+/HS- subjects
  - Day -56 to Day -29 relative to the first dose of inhaled study drug for Orkambi-/HS-, Orkambi-/HS+, and Orkambi+/HS+ subjects
- Run-in Period: Day -28 to Day -1 relative to the first dose of inhaled study drug (for Orkambi-/HS-, Orkambi-/HS+, and Orkambi+/HS+ subjects)
- Treatment Period
  - Treatment Period 1: Day 1 (first dose of inhaled study drug) through Day 28
  - Washout Period: Day 29 through Day 56
  - Treatment Period 2: Day 57 through Day 84

- Early Termination of Treatment Visit for a subject who discontinues from study drug treatment(s) and who does not complete the remaining assessments in the treatment period during which study drug treatment(s) is discontinued.
- Safety Follow-up Telephone Contact will occur 28 days (+ 3 days) after the Day 84 Visit; or 28 days (+ 3 days) after the Day 28 Visit for a subject who completes this visit but who will not be continuing into Treatment Period 2. (Note: Under certain circumstances, a safety Follow-up Telephone Contact may not be appropriate, and a Safety Follow-up Visit may be required.)
- A Safety Follow-up Visit will occur 28 days (+ 3 days) after a subject's last dose of study drug (whether inhaled study drug or lumacaftor/ivacaftor) in subjects who:
  - prematurely discontinue one or both study drugs during the course of either treatment period and do not complete the remaining assessments in the treatment period in which discontinuation occurred. In this circumstance, an ETT Visit is required in addition to the Safety Follow-up Visit (see Section 8.1.4).
  - have a clinical finding during the treatment period or during the 28-day Safety Follow-up Period that requires follow-up in the estimation of the PI. An ETT Visit may or may not be required in this circumstance (see Section 8.1.4).

Maintenance of Stable Medication Regimen for CF:

It is recommended that subjects remain on stable CF medication regimens from 28 days before Day 1 through the Safety Follow-up Telephone Contact with the exception of those subjects taking HS. Those subjects taking HS before the Screening Period will washout from HS during the Run-in Period from Day -28 to Day -1 and will not be allowed to take HS for through the Safety Follow-up Telephone Contact or Safety Follow-up Visit (other than as blinded inhaled study drug if allocated to a relevant treatment sequence). A stable medication regimen is defined as the current medication regimen that subjects have been following for at least 28 days before Day 1. Subjects are to be on stable CF medication (including Orkambi) for at least 28 days before dosing with inhaled study drug on Day 1.

Specific requirements apply to certain CF medications:

- Subjects must be on a stable regimen of lumacaftor/ivacaftor for a minimum of 28 days of treatment before the Day 1 Visit and continue this through the Safety Follow-up Telephone Contact.
- 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 Telephone Contact.
- 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 Telephone Contact. Inhaled cycling antibiotics should be administered in 28-day-on/28-day-off cycles.

  Clinic visits on Day 1 and Day 57 should be timed to occur **exactly** at the start of an on-cycle; treatment during the on-cycle should then end after **no more than** 28 days.

- 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 Telephone Contact.

  The first dose of inhaled study drug in each Treatment Period should coincide **exactly** with the first dose of the same cycled inhaled antibiotic (e.g., if TOBI is being administered first and Cayston second in the cycle, the Day 1 and Day 57 Visit should coincide with the first dose of TOBI).

8.1.1 Screening

Screening Visit assessments are listed in Table 3-1. All subjects will complete the Screening Visit.

Screening will occur between Day -28 and Day -1 for Orkambi+/HS- subjects, and between Day -56 and Day -29 for Orkambi-/HS-, Orkambi-/HS+, and Orkambi+/HS+ subjects. Screening will occur before the first dose of inhaled study drug to confirm that subjects meet the selection criteria for the study. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent and assent (where applicable) from each subject. During the Screening Visit it should be determined whether the subject will have a Run-in Period.

Table 8-2 outlines the assignment of subjects to a Run-in Period.

Table 8-2 Run-in Period Subject Assignment

Treatment at Screening Visit		Run-in Period[a]	HS	Source of Orkambi or Lumacaftor/Ivacaftor
Orkambi	HS			
+	-	No; subjects go directly from Screening to Day 1	N/A	Subjects will take their commercial Orkambi during the Screening Period, and will be given sponsor-supplied lumacaftor/ivacaftor starting on Day 1
+	+	Yes	Washout from HS	Subjects will take their commercial Orkambi during the Screening and Run-in Periods, and will be given sponsor-supplied lumacaftor/ivacaftor starting on Day 1
-	-	Yes	N/A	Subjects will be given sponsor-supplied lumacaftor/ivacaftor starting on the first day of the Run-in Period
-	+	Yes	Washout from HS	Subjects will be given sponsor-supplied lumacaftor/ivacaftor starting on the first day of the Run-in Period

[a] Subjects with a Run-in Period must complete both the Day -28 and Day -14 Visits. Further details about the Run-in Period are provided in Section 8.1.2.

To prepare for study participation, subjects will be instructed on the study restrictions and use of concomitant medications (Section 9.3 and Section 9.4).

8.1.1.1 Repetition of Screening Assessment(s)

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

- If there is clear evidence of a laboratory error (e.g., hemolyzed sample) or equipment malfunction, collection of a repeat sample for the appropriate laboratory test or assessment may be permitted with the approval of the medical monitor.
- Exclusionary liver function test (LFT) levels or plasma potassium levels, which may be retested within 14 days of the original screening date.

If screening spirometry measurements fail to meet acceptability and repeatability criteria as specified by American Thoracic Society/European Respiratory Society guidelines,[20] repeat spirometry evaluation may be performed once.

If repeat values of the individual assessment(s) are within the eligibility criteria and completed within the screening window, then the subject is eligible for the study.

8.1.1.2 Rescreening

Subjects may be rescreened after discussion with, and approval from, the medical monitor. If a subject is rescreened, all Screening Visit assessments will be repeated except for CF genotyping, follicle-stimulating hormone (FSH) level (if serum FSH level was ≥40 mIU/mL during prior screening), sweat chloride level, and the ophthalmologic examination (if the ophthalmologic examination was performed within the last 3 months before the Rescreening Visit). Subjects may only be rescreened once. 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 the Screening Period assessments (Section 8.1.1.1)
- Unexpected operational or logistic delays, or to meet the eligibility criteria
- Additional time to conduct ophthalmologic examinations (Section 11.6.5)

8.1.2 Run-in Period

Run-in Period assessments are listed in Table 3-2.

As described in Section 8.1.1, subjects who are not already being treated with commercially available Orkambi as part of their CF standard of care will enter the Run-in Period, which will occur between Day -28 and Day -1 before the first dose of inhaled study drug. These subjects will be provided with lumacaftor 200 mg/ivacaftor 125 mg tablets and are to take 2 tablets orally every 12 hours (q12h) with fat-containing food for a minimum of 28 days before dosing with inhaled study drug on Day 1.

Subjects who are receiving HS as part of their CF standard of care will washout from HS during the Run-in Period for at least 28 days before dosing with inhaled study drug on Day 1.

Note: For subjects who are taking commercially available Orkambi as part of their CF standard of care (Orkambi+/HS+ subjects), the last dose of commercially available Orkambi will be the

morning dose of the Day 1 Visit. For subjects who are being provided Orkambi by Vertex during the Run-in Period (Orkambi-/HS- and Orkambi-/HS+ subjects), the last dose of Orkambi during the Run-in Period will be the morning dose of the Day 1 Visit.

Study visits will occur on Day -28 and Day-14 relative to the first dose of inhaled study drug on Day 1.

8.1.3 Treatment Periods

Treatment Period assessments are listed in Table 3-3.

8.1.3.1 Treatment Period 1

The first dose of inhaled study drug will be administered after randomization on Treatment Period 1 Day 1. This must also be the first "on" day for single cycled inhaled antibiotics (e.g., TOBI) and the first day of a new "on" period for an inhaled antibiotic in a continuous alternating regimen,

Inhaled study drug should be taken according to instructions provided. Study visits will occur on Day 1, Day 14, and Day 28. On Day 3, subjects will have a telephone contact for safety purposes (e.g., inquire about AEs). The last dose of inhaled study drug in Treatment Period 1 is the dose of inhaled study drug received at the Day 28 Visit.

Note: All subjects, whether they are taking commercially available Orkambi or Vertex-supplied Orkambi, must take a dose of Orkambi on the morning of the Day 1 Visit. All remaining doses of lumacaftor/ivacaftor for the duration of the study will be supplied by Vertex at the Day 1 Visit (see Section 10.2.2).

8.1.3.2 Washout Period

Subjects will undergo a Washout Period of 28 days (+ 3 days) between the 2 Treatment Periods and must have at least 14 days in their "off-period" for inhaled single cycled antibiotics or at least 14 days of the "alternate" antibiotic for a continuous cycled 2 antibiotic regimen.

The Washout Period may be extended for acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics); extension of the Washout Period must be discussed with the medical monitor.

8.1.3.3 Treatment Period 2

The first dose of inhaled study drug in Treatment Period 2 will be administered at the Day 57 Visit. This must also be the first "on" day for single cycled inhaled antibiotics (e.g., TOBI) and the first day of a new "on" period for an inhaled antibiotic in a continuous alternating regimen, provided that at least 14 days have elapsed with no inhaled antibiotic (single cycled regimen) or the other antibiotic (continuous cycling of 2 antibiotics).

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 28 days before the Day 57 Visit (first dose of inhaled study drug in Treatment Period 2) and must not have any "non-CF-related" illness within 2 weeks before the Day 57 Visit (first dose of inhaled 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 medical monitor.

Inhaled study drug should be taken according to instructions provided. The last dose of inhaled study drug in Treatment Period 2 is the dose of inhaled study drug at the Day 84 Visit.

Study visits will occur on Day 57, Day 70, and Day 84. On Day 59, subjects will have a telephone contact for safety purposes (e.g., inquire about adverse events).

8.1.4 Early Termination of Treatment

A subject who prematurely discontinues inhaled study drug will continue to take lumacaftor/ivacaftor. Conversely, a subject who discontinues lumacaftor/ivacaftor will continue to take inhaled study drug. Subjects who prematurely discontinue one or both study drugs will be asked to complete the remaining assessments in the treatment period during which treatment was discontinued. If all assessments are completed, an ETT Visit is not required.

A subject who discontinues from study drug treatment(s) and who does not complete the remaining assessments in the treatment period during which study drug treatment(s) is discontinued is required to complete an ETT Visit, which is to be scheduled as soon as possible after it is confirmed that the subject does not intend to complete the remaining assessments.

A subject who prematurely discontinues from one or both study drugs in Treatment Period 1 will not continue into Treatment Period 2.

If the ETT Visit occurs 28 days or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit (Section 8.1.6), and neither a Safety Follow-up Visit nor a Safety Follow-up Telephone Contact is required.

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.

8.1.5 Safety Follow-up Telephone Contact

The Telephone Contact is a phone interview for the purpose of collecting information on AEs. A Safety Follow-up Telephone Contact is scheduled to occur 28 days (+3 days) after the Day 84 Visit for subjects who complete this visit, or 28 days (+3 days) after the Day 28 Visit for subjects who complete this visit but who will not be continuing into Treatment Period 2 (see Section 8.1.4).

Under certain circumstances, a safety Follow-up Telephone Contact may not be appropriate, and a Safety Follow-up Visit may be required, as delineated in Section 8.1.6.

8.1.6 Safety Follow-up Visit

Safety Follow-up Visit assessments are listed in Table 3-4.

A Safety Follow-up Visit will occur 28 days (+ 3 days) after a subject's last dose of study drug (whether inhaled study drug or lumacaftor/ivacaftor) in subjects who:

- prematurely discontinue one or both study drugs during the course of either treatment period and do not complete the remaining assessments in the treatment period in which discontinuation occurred. In this circumstance, an ETT Visit is required in addition to the Safety Follow-up Visit (see Section 8.1.4).

- have a clinical finding during the treatment period or during the 28-day Safety Follow-up Period that requires follow-up in the estimation of the PI. An ETT Visit may or may not be required in this circumstance (see Section 8.1.4).

8.1.7 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 with the primary goal of evaluating the safety of the inhaled study drug regimen to ensure the subjects' safety (Section 12.3.4). Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be included in the IDMC charter.

8.2 Rationale for Study Design and Study Drug Regimens

8.2.1 Study Design

This Phase 2a, randomized, double-blind, placebo-controlled, incomplete block, crossover, multicenter study in subjects ≥12 years of age with CF who are homozygous for the *F508del-CFTR* mutation and receiving stable Orkambi treatment is designed to evaluate the safety, efficacy, and PK of treatment with VX-371 in 4.2% HS compared to 4.2% HS alone.

A randomized, double-blind, placebo-controlled study design was selected to avoid observer bias and reduce symptoms or outcomes arising from the investigator's or the subject's knowledge of treatment. A crossover design in which subjects are randomized to 1 of 4 treatment sequences will enable within-subject comparison of selected treatment effects with increased statistical power. A 28-day washout period is judged to be of sufficient duration for all subjects to return to their baseline values for FEV_1 and to accommodate synchronization with cycling inhaled antibiotics.

There are 2 primary endpoints; the first is to evaluate safety and tolerability, and the second is to evaluate efficacy as measured by the absolute change in $ppFEV_1$ from study baseline at Day 28 in each Treatment Period. Although the primary objectives are to evaluate the safety and efficacy of VX-371 in 4.2% HS versus 4.2% HS alone, 2 additional treatment sequences will compare VX-371 in 0.17% saline (placebo) versus 0.17% saline (placebo). These comparisons will provide insight with respect to the effect of VX-371 alone and inform design options for future studies. Even though 2 different concentrations of saline will be used, the double-blind will be maintained with respect to VX-371 because allocation to this component will remain unknown to both investigators and subjects.

A sample size of approximately 150 subjects is considered feasible and is expected to provide sufficient data to evaluate the efficacy, safety, and PK of VX-371 formulated with and without HS. The unbalanced randomization ratio permits more subjects to be used to address the primary study objective.

8.2.2 Study Drug Dose and Duration

[redacted]

Thus, the current study is designed to demonstrate safety and efficacy of an 85 µg dose of VX-371 administered bid by oral inhalation in subjects with CF.

Parion Study PS-G201 is an ongoing randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of 85 µg VX-371 bid in subjects with CF. The recommendations of a planned IDMC review of safety data indicated that no safety-related changes to the study conduct were needed and supported enrollment of pediatric subjects 12 to 17 years of age. Further, the nonclinical safety toxicology data (see the VX-371 Investigator's Brochure for details) supports 28 days of continuous treatment of VX-371 in the current study.

8.2.3 Rationale for Study Assessments

Spirometry: Lung function in CF declines with age and is a significant predictor of mortality.[21] Spirometry (as measured by FEV) is the most widely implemented standardized assessment to evaluate lung function.[22,23] FEV_1 obtained from spirometry is a reflection of the extent of airway obstruction and, as the most clinically accepted measure of disease progression in CF, is the recommended primary clinical endpoint in efficacy studies for CF.

[redacted]

9 STUDY POPULATION

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

9.1 Inclusion Criteria

Subjects who meet all of the following inclusion criteria will be eligible.

1. Subject (or subject's legally appointed and authorized representative) will sign and date an informed consent form (ICF) and, where appropriate, assent form.
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Willing and able to use the nebulization device as directed by the study manual.
4. Subjects (male and female) will be aged 12 years or older on the date of ICF or, where appropriate, date of assent.
5. Subjects with confirmed diagnosis of CF,[36] defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis. A sweat chloride test must be performed at the Screening Visit if an eligible sweat chloride value is not available in the subject's medical records and the Screening Visit value is needed to establish eligibility. For subjects using sweat chloride values documented in their medical records to establish eligibility, the sweat chloride test at the Screening Visit is optional. If both results are available, the result from the Screening Visit will be used to determine eligibility.
6. Subjects who are homozygous for *F508del-CFTR*. If the *CFTR* screening genotype result is not received before randomization, a previous *CFTR* genotype lab report may be used to establish eligibility. *Note: Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study as described in Section 9.5*.
7. Subjects with ppFEV$_1$ of ≥40 to <90 percentage points adjusted for age, sex, and height according to the Global Lung Initiative (GLI)[37] at the Screening Visit.
8. Subjects with stable CF disease as deemed by the investigator.
9. Subjects who are willing to remain on a stable CF medication regimen through the Safety Follow-up Telephone Contact.
10. Subjects who are willing to discontinue physician-prescribed HS use.
11. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit. Females of childbearing potential must have a negative urine pregnancy test at the Day 1 Visit before receiving the first dose of inhaled study drug.
12. Subjects of childbearing potential and who are sexually active must meet the contraception requirements outlined in Section 11.6.7.1.

9.2 Exclusion Criteria

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

1. History of any comorbidity, which in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject. For example, clinically significant adrenal disease, or any present history of any clinically significant and uncontrolled neurologic, gastrointestinal, renal, hepatic, cardiovascular (including hyper/hypotension and tachy/bradycardia), psychological, pulmonary (other than

CF), metabolic, endocrine, or hematological disorder or disease, or any other major disorder or disease, in the opinion of the investigator.

2. Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject (as deemed by the investigator).
3. Any of the following abnormal laboratory values at the Screening Visit:
   - Hemoglobin <10 g/dL
   - Abnormal liver function defined as any 2 or more of the following:
     - ≥3 × upper limit of normal (ULN) aspartate aminotransferase (AST)
     - ≥3 × ULN alanine aminotransferase (ALT)
     - ≥3 × ULN gamma-glutamyl transpeptidase
     - ≥3 × ULN alkaline phosphatase
   - ALT or AST >5 × ULN
   - Total bilirubin >2 × ULN
   - Abnormal renal function, defined as creatinine clearance rate <50 mL/min/1.73 m^2 using the Bedside Schwartz equation[38] (for subjects 12 to 17 years of age) or <50 mL/min using the Cockcroft-Gault equation[39] (for subjects ≥18 years of age)
   - Plasma potassium >ULN
4. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of inhaled study drug).
5. A 12-lead ECG demonstrating QTcF >450 msec at the Screening Visit. If QTcF exceeds 450 msec for the screening ECG, the ECG should be repeated 2 more times during the Screening Period, and the average of the 3 QTcF values should be used to determine the subject's eligibility.
6. History of solid organ or hematological transplantation.
7. Used diuretics (including amiloride) or renin-angiotensin aldosterone system antihypertensive drugs (spironolactone, angiotensin converting enzyme [ACE] inhibitors, or angiotensin receptor blockers [ARBs]), drospirenone, or trimethoprim in the 28 days prior to Screening or an anticipated need for any of these medications during the study.
8. Ongoing or prior participation in an investigational drug study within 30 days of the Screening Visit.
   - A washout period of 5 terminal half-lives of the previous investigational study drug, or 30 days, whichever is longer, must elapse before the Screening Visit.
   - The duration of the elapsed time may be longer if required by local regulations.

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

9. Inability to withhold short-acting, long-acting, or once-daily, long-acting bronchodilator use for 4, 12, or 24 hours prior to clinic visit, respectively.
10. History of significant intolerance to inhaled HS.
11. Known hypersensitivity or history of intolerance to Orkambi.
12. Known hypersensitivity to the VX-371 or amiloride.
13. Use of restricted medication or food within specified duration before the first dose of study drug as defined in Section 9.3.
14. Pregnant and nursing females.
15. Subjects who have participated in Parion Sciences Study PS-G201.
16. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study.

9.3 Study Restrictions

Prohibited medications and certain foods are not allowed in this study (Screening Period through Safety Follow-up Telephone Contact) as summarized in Table 9-1. A non-exhaustive list of study prohibitions and cautions for food and medication will be provided in the Study Reference Manual.

Table 9-1 Study Restrictions

	Study Period	
Restricted Medication/Food	**Screening Period**	**Treatment Period Through Safety Follow-up Telephone Contact**
Strong CYP3A inducers	None allowed within 14 days before the first dose of study drug	None allowed
Strong CYP3A inhibitors	• For subjects who have been receiving Orkambi as background therapy for at least 7 days before the Screening visit, there is no restriction • For all others, none allowed within 14 days before the first dose of lumacaftor/ivacaftor	Use with caution
Hypertonic saline	None allowed within 28 days before the first dose of inhaled study drug	None allowed
Diuretics (including amiloride)	None allowed	None allowed
Renin-angiotensin antihypertensive drugs (e.g. spironolactone, angiotensin-converting-enzyme (ACE) inhibitors, or angiotensin receptor blockers)	None allowed	None allowed

Table 9-1 Study Restrictions

	Study Period	
Restricted Medication/Food	**Screening Period**	**Treatment Period Through Safety Follow-up Telephone Contact**
Drospirenone	None allowed within 14 days before the first dose of inhaled study drug	None allowed
Trimethoprim	None allowed within 14 days before the first dose of inhaled study drug	None allowed

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

9.4 Prior and Concomitant Medications

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

- Subjects must remain on a stable medication (and supplement) regimen for their CF from the Run-in Period through the Day 84 Visit, and, if applicable, through the Safety Follow-up Telephone Contact. Stable medication regimen is defined as the current medication regimen for CF that subjects have been following for at least 28 days before the Day 1 Visit; this includes treatment with Orkambi but excludes treatment with HS. Subjects must not initiate long-term treatment with new medication from 28 days before the Day 1 Visit through the Safety Follow-up Telephone Contact unless it is discussed and approved by the medical monitor. Guidelines for stable inhaled antibiotic regimens for CF are as follows:
  - Subjects who are taking daily inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
  - Subjects who are on inhaled cycling antibiotics should continue on their prior schedule. The timing of the first dose of inhaled study drug in Treatment Periods 1 and 2 (i.e., the Day 1 and Day 57 Visits, respectively) should be timed to occur **exactly** at the start of an on-cycle synchronized; treatment during the on-cycle should then end after **no more than** 28 days.
  - Subjects who alternate 2 different antibiotics monthly should remain on the same schedule during the study. The timing of the first dose of inhaled study drug in each Treatment Period should coincide **exactly** with the first dose of the same cycled inhaled antibiotic (e.g., if TOBI is being administered first and Cayston second in the cycle, the Day 1 and Day 57 Visit should coincide with the first dose of TOBI).
- Information about bronchodilator use during the study will be collected and documented. Subjects who are using a bronchodilator must have their spirometry assessments performed according to the guidelines provided in Section 11.5.1.

9.4.1 Prohibited Medications

Prohibited medications are described in Table 9-1.

The use of cytochrome P450 (CYP) 3A substrates is not prohibited in this study, but investigators need to be aware that lumacaftor appears to be a strong inducer of this CYP isoenzyme. Therefore, the efficacy of drugs extensively metabolized by this isoenzyme may be affected. Each investigator should evaluate the benefit/risk ratio of using such drugs with lumacaftor during this study. Investigators should discuss any concerns regarding the use of CYP3A substrates during this study with the medical monitor.

The use of CYP2C and 2B6 substrates are not prohibited in this study, but investigators need to be aware that lumacaftor has been shown in vitro to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19; inhibition of CYP2C8 and CYP2C9 has also been observed in vitro. Additionally, in vitro studies suggest that ivacaftor may inhibit CYP2C9. Therefore, concomitant use of lumacaftor in combination with ivacaftor with CYP2B6, CYP2C8, CYP2C9, and CYP2C19 substrates may alter the exposure of these substrates. Each investigator should evaluate the benefit to risk ratio of using such drugs with lumacaftor and ivacaftor during this study and discuss the use of these substrates during this study with the medical monitor.

A non-exhaustive study prohibitions and cautions list for food and medications will be provided in the Study Reference Manual.

9.5 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. 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 prematurely discontinue study drug treatment should continue to return for study assessments, as noted in Section 8.1.4.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit, if applicable (see Section 8.1.4), and follow up with the subject regarding any unresolved AEs.

Subjects who are randomized on the basis of a historical genotyping lab result and whose screening genotype does not confirm eligibility will be discontinued from study drug treatment. These subjects will undergo ETT and/or Safety Follow-up Visits per Sections 8.1.4 and 8.1.6, and will then be discontinued from the study. After discontinuation from study drug treatment, these subjects will not undergo any further assessments other than those performed at the ETT and/or Safety Follow-up Visits.

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 withdrawn from study drug treatment for any of the following reasons:

- Vertex, regulatory authorities, or the site's institutional review board (IRB) or independent ethics committee (IEC) close the study.
- A female subject or a female partner of a male subject has a confirmed pregnancy.
- A subject has persistent and severe bronchospasm related to study drug administration.
- Development of a life-threatening AE or a serious adverse event (SAE) that places him/her at immediate risk, and discontinuation of study treatment deemed necessary.

A subject may be withdrawn from study drug treatment after a discussion between the investigator and the medical monitor for any of the following reasons:

- Development of a medical condition that requires prolonged concomitant therapy with a prohibited medication or prolonged interruption of the study drug.
- Noncompliance with study requirements.
- An increase in transaminases (ALT or AST) according to evaluations and management described in Section 11.6.2.1.
- A potassium level >ULN. A confirmatory potassium level may be drawn at the discretion of the investigator before making the decision to remove a subject from the study. Refer to Section 11.6.2.2 for further guidance on treatment of hyperkalemia.

9.6 Replacement of Subjects

Subjects who withdraw or are withdrawn during the Screening or Run-in periods may be replaced at the discretion of the Sponsor. 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

10.2.1 Nebulizer

Inhaled study drug will be administered bid approximately 10 to 12 hours apart (Section 8.2.2) by a PARI eFlow nebulizer. The nebulizer device (nebulizer and handset) will be provided to the subject for use with the inhaled study drug at the Day 1 Visit. This nebulizer has been customized to be used only with the inhaled study drug and is not to be used for the inhalation of other treatments. Additionally, it is important that the subjects use the provided nebulizer for inhalation of study drug and not use any other PARI eFlow devices that they may have.

Subjects will be given instruction by the site staff on the proper use and care of the nebulizer, and will also receive written instructions on the care, use, and cleaning requirements. The nebulizer device identification information will be documented for each subject. A new nebulizer handset will be provided for replacement at the Day 57 Visit.

Subjects are required to use the correctly assembled device, into which inhaled study drug has been added, and to nebulize through oral inhalation while sitting up, with the device held horizontally and breathing more deeply than normal tidal breathing. This should be continued until the nebulizer device indicates that all inhaled study drug has been delivered.

A replacement nebulizer and/or handset may be provided at other times during the study if necessary (Section 10.9).

10.2.2 Lumacaftor in Combination With Ivacaftor

All subjects are to be on a stable regimen of lumacaftor/ivacaftor for at least 28 days before the Day 1 Visit and are to continue taking lumacaftor/ivacaftor through the Safety Follow-up Telephone Contact.

Subjects who are taking commercially available Orkambi at Screening (i.e., Orkambi+/HS- and Orkambi+/HS+ subjects) will continue to take their commercially available Orkambi during the Screening Period. Subjects who are Orkambi+/HS+ will continue to take their commercially available Orkambi during the Run-in Period while they washout from HS. The last dose of commercially available Orkambi for Orkambi+/HS- and Orkambi+/HS+ subjects will be the morning dose of the Day 1 Visit.

Subjects not already being treated with commercially available Orkambi (i.e., Orkambi-) will be provided with lumacaftor/ivacaftor by Vertex at the start of the Run-in Period and must continue to take it for the remainder of the study (i.e., through the Safety Follow-up Telephone Contact); for these subjects, the last dose of lumacaftor/ivacaftor during the Run-in Period will be the morning dose of the Day 1 Visit.

All subjects, whether they are taking commercially available Orkambi or Vertex-supplied lumacaftor/ivacaftor, must take a dose of Orkambi on the morning of the Day 1 Visit. All remaining doses of lumacaftor/ivacaftor for the duration of the study (i.e., through Safety Follow-up Telephone Contact) will be supplied by Vertex at the Day 1 Visit. Subjects must not take both commercially available Orkambi and Vertex-supplied lumacaftor/ivacaftor (i.e., double dosing must be avoided).

Subjects are to take 2 tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) orally q12h with fat-containing food. Examples of appropriate fat-containing foods include eggs, avocados, nuts, butter, peanut butter, cheese pizza, whole-milk dairy products (such as whole milk, cheese, and yogurt), etc. If a subject misses a dose and remembers the missed dose within 6 hours, the subject should take the dose with fat-containing food. If more than 6 hours elapsed after the usual dosing time, the subject should skip that dose and resume the normal schedule for the following dose. A double dose should not be taken to make up for the forgotten dose (Section 10.6.2).

Arrangements will be made for the return of any unused lumacaftor/ivacaftor for final accountability (refer to the Pharmacy Manual for more detail).

10.3 Method of Assigning Subjects to Treatment Groups

Approximately 150 subjects will be randomized to 1 of 4 treatment sequences when they are determined to have met all eligibility criteria. Subjects will be randomized in a 2:2:1:1 ratio (VX-371 + 4.2% HS versus 4.2% HS; 4.2% HS versus VX-371 + 4.2% HS; VX-371 + placebo versus placebo; placebo versus VX-371 + placebo), stratifying for $ppFEV_1$ severity (<70% or ≥70%).

Randomization must only occur after all inclusion and exclusion criteria are met and before the first dose of inhaled study drug.

An interactive web response system (IWRS) will be used to assign subjects to treatment sequence. Detailed instructions for randomization will be provided separately.

10.4 Dose Modification for Toxicity

Modifications of study drug doses are prohibited. Interruptions of study drug dosing should be discussed with the medical monitor and may be considered on a case-by-case basis after discussion with the medical monitor. Specific instructions for interruption for elevated LFTs and plasma potassium are provided in Section 11.6.2.

10.5 Study Drug Interruption

If study drug dosing must be interrupted for more than 72 hours, the medical monitor must be notified. In these instances, study drug dosing may only resume after signed approval by the medical monitor. Specific instructions for interruption for prohibited medications, elevated LFT levels, and hyperkalemia are provided in Sections 9.3 and 9.4.1, Section 11.6.2.1, and Section 11.6.2.2, respectively.

10.6 Missed Doses

10.6.1 Inhaled Study Drug

On Non-Study Visit Days:

- If a subject misses a dose of inhaled study drug and remembers the missed dose within 6 hours, the subject should take the dose of inhaled study drug.
- If more than 6 hours elapsed after the usual dosing time, the subject should skip that dose of inhaled study drug and resume the normal schedule for the following dose. A double dose should not be taken to make up for the forgotten dose.

On Study Visit Days (Afternoon Visits Only):

- If a subject misses a dose of inhaled study drug and remembers the missed dose within 6 hours of an afternoon study visit, the subject should NOT take the missed dose. If the missed dose is taken within 6 hours of the study visit, the subject should alert site personnel upon arrival to the site.

10.6.2 Lumacaftor in Combination With Ivacaftor

If a subject misses a dose of lumacaftor/ivacaftor and remembers the missed dose within 6 hours, the subject should take the dose with fat-containing food. If more than 6 hours elapses after the usual dosing time, the subject should skip that dose and resume the normal schedule for the following dose. A double dose should not be taken to make up for the forgotten dose.

10.7 Packaging and Labeling

Inhaled study drug (85 µg VX-371 in 4.2% HS; 4.2% HS; 85 µg VX-371 plus 0.17% saline [placebo]; and placebo [0.17% saline]) will be supplied by Vertex in blow-fill seal vials that are filled to deliver 3 mL of inhaled study drug.

Vertex will supply the lumacaftor 200-mg/ivacaftor 125-mg tablets in child-resistant weekly blister cards. Study drug labeling will be in compliance with applicable local and national

regulations. Additional details regarding packaging, labeling, and dispensing for inhaled study drug and Orkambi will be included in the Pharmacy Manual.

10.8 Study Drug Supply, Storage, and Handling

Table 10-1 provides the study drug information. The investigator or an authorized designee (e.g., a licensed pharmacist) will ensure that all investigational product is stored in a secured area under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for as detailed in Section 10.9.

Table 10-1 Study Drug

Drug Name	Formulation/ Route	Dosage	Packaging	Storage Condition
Placebo	Liquid/ oral nebulized inhalation	3 mL 0.17% saline	Supplied as 3 mL blow-fill seal vials	25°C (77°F) with excursions permitted from 15 to 30°C (59 to 86°F)
Hypertonic saline (HS)	Liquid/ oral nebulized inhalation	3 mL 4.2% HS	Supplied as 3 mL blow-fill seal vials	25°C (77°F) with excursions permitted from 15 to 30°C (59 to 86°F)
VX-371	Liquid/ oral nebulized inhalation	85 µg VX-371 in 3 mL 0.17% saline	Supplied as 3 mL blow-fill seal vials	25°C (77°F) with excursions permitted from 15 to 30°C (59 to 86°F)
VX-371 + HS	Liquid/ oral nebulized inhalation	85 µg VX-371 in 3 mL 4.2% HS	Supplied as 3 mL blow-fill seal vials	25°C (77°F) with excursions permitted from 15 to 30°C (59 to 86°F)
Lumacaftor/ ivacaftor (fixed-dose)	Fixed-dose tablet/ oral	400-mg lumacaftor/ 250-mg ivacaftor	Supplied as 200-mg lumacaftor/125-mg ivacaftor tablets	Store at ≤30°C (86°F)

10.9 Drug Accountability

The pharmacist or designated study site staff will maintain records documenting the dates and amounts of (1) study drug received; (2) study drug dispensed to and returned by the subjects; and (3) nebulizer and nebulizer handsets dispensed to and returned by the subjects. Subjects will be instructed to return all used and unused materials associated with the study drugs 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.

10.10 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subjects until the study monitor has performed drug accountability. At the end of the study, the study monitor will provide instructions as to the disposition of any unused investigational product. If the study monitor authorizes destruction at the study site, the investigator will ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Vertex. Destruction will be adequately documented.

Procedures for destruction or return of the inhaled study drug and Vertex-supplied lumacaftor/ivacaftor will be detailed in the Pharmacy Manual.

10.11 Compliance

To maximize treatment compliance during the study, the investigator or designee will supervise inhaled study drug dosing and nebulizer use at each visit. At each visit, site personnel will review subject compliance with study drug dosing and remind the subject of study drug dosing requirements. Compliance will also be assessed by ongoing study drug count.

If a subject demonstrates continued noncompliance of study drug dosing despite educational efforts, the investigator should contact the medical monitor to discuss discontinuation of the subject from the study treatment.

10.12 Blinding and Unblinding

This is a double-blind study.

10.12.1 Blinding

The subjects and all site personnel, including the investigator, the site monitor, and the study team, will be blinded with the exception of the following:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the subject and the fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations
- External vendor (unblinded) statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IXRS Management for IXRS oversight and system administration
- IDMC
- Vendor preparing the unblinded analysis for the IDMC
- The bioanalytical external vendor personnel assigned to the study and Vertex Bioanalysis CRO Monitors who will not be participating in the study team
- The medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time

Spirometry Data Blinding

Despite treatment blinding, knowledge of the spirometry results has the potential to suggest whether a subject has been administered active inhaled study drug or placebo. Therefore, during the conduct of the study, the Vertex study team will have no access to the postdose spirometry data. The vendor for central reading of the spirometry data will send only the blinded spirometry files (blinded treatment group, with real values for screening and baseline, but with dummy values for all the spirometry assessments after baseline) to Vertex to be used for developing the statistical programs. Furthermore, subjects and their caregivers should not be informed of their

study-related spirometry results during the Treatment Period regardless of whether the subject has prematurely discontinued treatment.

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

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

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

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor will be notified within 24 hours of the unblinding event. The reason and the date of the unblinding will be documented clearly in the subject's study file. Information about the treatment assignment obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with the sponsor (Vertex), contract research organization (CRO), or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS or designee, per Section 13.1.

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, Table 3-3, and Table 3-4.

[redacted]

Subjects who have taken their morning dose of inhaled study drug on the day of a study visit may have their study visit and undergo visit assessments provided that the predose assessments do not occur within 6 hours of the morning dose of inhaled study drug.

11.2 Subject and Disease Characteristics

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

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

11.3 Pharmacokinetics

11.3.1 Blood Sampling

At the visits and time points indicated in Table 3-3 and Table 3-4, blood samples for PK analysis will be collected for the determination of the concentrations of VX-371, [redacted]. Blood samples collected before dosing must be collected within 90 (+ 5) minutes before dosing. The acceptable windows for blood PK sampling time points are detailed in Table 11-1.

Samples from the PK sampling will be kept frozen by Vertex or its designee until all analyses have been completed and then disposed of according to Vertex or designee standard operating procedures.

For each visit with a PK blood draw, a record of study drug administration will be collected. The collection date and time that each PK blood sample is drawn will also be recorded.

Table 11-1 Acceptable Blood PK Sampling Windows

Sampling Time	Time From Sampling Schedule Allowed
Predose	Within 90 (+ 5) minutes before inhaled study drug dose on PK sampling days
60 minutes after completion of inhaled study drug dosing	± 30 minutes

11.3.2 Urine Sampling

Urine samples for PK analysis will be collected according to Table 3-3 and Table 3-4.

Urine samples will be collected for determination of urine levels of VX-371. Urine samples collected before dosing must be collected within 90 (+ 5) minutes before dosing. The acceptable windows for urine PK sampling time points are detailed in Table 11-2.

Samples will be shipped to a Vertex designated laboratory via a central laboratory and analyzed with a validated method for the quantification of VX-371. The date and time of urine sampling will be collected as well as the date and time of the last dose of inhaled study drug taken before collection of the urine sample.

Table 11-2 Acceptable Urine PK Sampling Windows

Sampling Time	Time From Sampling Schedule Allowed
Predose	Within 90 (+ 5) minutes before inhaled study drug dose on PK sampling days

Table 11-2 Acceptable Urine PK Sampling Windows

Sampling Time	Time From Sampling Schedule Allowed
90 minutes after completion of inhaled study drug dosing	± 60 minutes

11.3.3 Processing and Handling of Pharmacokinetic Samples

Detailed procedures for the collection of blood and urine samples and further procedures for processing and handling of samples for PK analysis will be provided in the Sample Handling Guideline. The shipment address and assay laboratory contact information will be provided to the investigational site before initiation of the study.

11.3.4 Bioanalysis

Samples will be analyzed using a validated analytical method in compliance with Vertex or designee standard operating procedures. A description of the assay and validation data will be provided in separate reports.

[redacted]

11.5 Efficacy

11.5.1 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines[20] at the time points noted in Table 3-1, Table 3-2, Table 3-3, and Table 3-4 according to the additional guidelines that follow.

During the Treatment Period, spirometry will be performed within 60 (± 10) minutes before and 30 (± 5) minutes after dosing with inhaled study drug. Spirometry assessments should be performed as closely as possible to the same time of day as the baseline assessments to minimize the impact of diurnal variation.

With the exception of the Screening Visit, all predose spirometry assessments should be performed pre-bronchodilator. At the Screening Visit, the spirometry assessment may be performed pre- or post-bronchodilator. Pre-bronchodilator spirometry is defined as spirometry testing performed for subjects who have

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

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

- If a subject's Day 1 predose spirometry is pre-bronchodilator, but on a subsequent visit, the subject forgets to withhold bronchodilator use, a post-bronchodilator spirometry will be obtained for that visit only, and the visit will not be rescheduled. Spirometry during subsequent visits will be performed as pre-bronchodilator assessments.
- If on Day 1, the subject forgets to withhold his/her dose of bronchodilator, spirometry should be performed post-bronchodilator and all subsequent spirometric measurements (according to the Schedule of Assessments detailed in Section 3) should be performed post-bronchodilator.
- Each spirometry assessment will be recorded in the source documents as pre-bronchodilator or post-bronchodilator.

If, in the opinion of the investigator, pretreatment with a short-acting bronchodilator is needed before administration of inhaled study drug, this may be done in the clinic before the dose of inhaled study drug is administered but after the predose spirometry assessment has been completed.

The parameters listed below will be normalized using the GLI:[37]

- FEV_1 (L)
- Forced vital capacity (FVC) (L)
- FEV_1/FVC (ratio)

- Forced expiratory flow ($FEF_{25\%-75\%}$) (L/s)

All sites will be provided with spirometers and associated materials to be used for all study assessment by the central spirometry service. Spirometry data will be transmitted to a centralized spirometry service for quality review.

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

[redacted]

[redacted]

11.6 Safety

Safety evaluations will include AEs, spirometry, clinical laboratory assessments of serum, plasma, and urine, clinical evaluation of vital signs, ECGs, physical examinations, and ophthalmologic examinations (for pediatric subjects <18 years of age only).

11.6.1 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.

11.6.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory with the exception of urine pregnancy tests, which will be analyzed locally. Although blood samples are to 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 the mandatory liver function testing (Section 11.6.2.1).

Blood and urine samples for clinical laboratory assessments will be collected as shown in Table 3-1, Table 3-3, and Table 3-4. Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1.1).

The safety laboratory test panels are shown in Table 11-3.

Table 11-3 Safety Laboratory Test Panels

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

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

Clinical laboratory assessments from screening will have no clinically significant findings that preclude participation in the study, as judged by the investigator, for a subject to receive inhaled study drug on Day 1.

Pregnancy (β-human chorionic gonadotropin) Tests for Females of Childbearing Potential: Serum samples will be obtained as specified in Table 3-1 and analyzed at the central laboratory. Urine pregnancy tests will be performed at the site as specified in Table 3-3 and Table 3-4. The urine pregnancy test on Day 1 must be negative before the first dose of inhaled study drug.

If a urine pregnancy test is positive, all study drug dosing will be stopped and the pregnancy will be confirmed with a serum β-human chorionic gonadotropin test. If confirmed, the pregnancy will be reported and the subject will be permanently withdrawn from study drug dosing as discussed in Section 11.6.7.2. If a pregnancy test is positive, the procedures outlined in Section 11.6.7.2 will be followed.

FSH (Screening Period only): Blood sample for FSH will be measured for any potentially postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be ≥40 mIU/mL to be considered postmenopausal.

CFTR genotype (Screening Period only): *CFTR* genotyping will be performed to confirm the subject is homozygous for *F508del-CFTR. Note: 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.

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

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

11.6.2.1 Elevation of Liver Function Test Parameters

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 performed by the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT and AST levels, as clinically indicated. If a subject cannot return to the site for liver function testing, a local laboratory may be used. Elevations in LFTs at the local laboratory must be reported immediately to the medical monitor, and the subject must have the tests repeated and sent to the central laboratory as soon as possible (ideally within 48 to 72 hours).

Study Drug Interruption

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

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

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

If no convincing alternative etiology (e.g., acetaminophen use, viral hepatitis, or alcohol ingestion) for the elevated transaminases is identified, regardless of whether ALT or AST levels have improved, study drug treatment must be discontinued, in consultation with the medical monitor. Subjects in whom treatment is discontinued for elevated transaminases should have their transaminases monitored closely until levels normalize or return to baseline.

Resumption of Study Drug

If a convincing alternative etiology is identified for the elevated transaminases (ALT, AST, gamma glutamyl transpeptidase, alkaline phosphatase, and total bilirubin), study drug may be resumed when transaminases return to baseline or are ≤2 × ULN, whichever is higher. Approval of the medical monitor is required before resumption of study drug. Upon resumption of study drug, transaminases must be assessed weekly for 4 weeks. If a protocol-defined transaminase elevation occurs within 4 weeks of rechallenge with the study drugs, then the study drugs must be discontinued, regardless of the presumed etiology.

11.6.2.2 Hyperkalemia

Subjects with a potassium level that is ≤0.4 units below the ULN at the Day 1 or Day 57 Visit will be required to have a blood sample collected for a repeat evaluation of plasma potassium within 7 (± 2) days.

The standard of care for management of hyperkalemia should be applied. A thorough investigation of potential causes should be conducted, and the subject's potassium level should be followed closely.

If hyperkalemia occurs, inhaled study drug should be interrupted until the plasma potassium has stabilized in the normal range. If no convincing temporary or possibly reversible alternative etiology (e.g., oral intake of potassium, acute renal failure, metabolic acidosis, uncontrolled diabetes mellitus, admission of repeated fist-clenching during phlebotomy, hemolyzed sample) for the elevated potassium is identified, study drug treatment must be discontinued regardless of whether the level has improved; this decision should be made in consultation with the medical monitor. Subjects in whom treatment is discontinued for elevated potassium should have their potassium levels monitored closely until levels normalize or return to baseline.

11.6.3 Physical Examinations and Vital Signs

A full physical examination of all body systems and vital signs assessment will be performed at the Screening Visit, ETT Visit, and Safety Follow-up Visit (see Table 3-1 and Table 3-4). At other visits, abbreviated physical examinations will be performed before dosing with inhaled study drug (see Table 3-3).

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.

The abbreviated physical examination will include an assessment of the following body systems: head/neck/thyroid, EENT, cardiovascular system, respiratory system, skin, and abdomen.

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

11.6.4 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout according to the Schedule of Assessments (Table 3-1, Table 3-3, and Table 3-4). Additional standard 12-lead ECGs will be performed at any other time if clinically indicated. During the Treatment Period,

the ECG will be performed 60 (± 30) minutes after the completion of inhaled study drug dosing. The performance of all ECGs will adhere to the following:

- The subject will be instructed to rest in the seated or supine position for at least 5 minutes before having an ECG performed.

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

To ensure safety of the subjects, a qualified individual at the study site will make comparisons to baseline measurements. If the QTcF is increased by >45 msec from the baseline or an absolute QTcF value is ≥500 msec for any scheduled ECG, 2 additional ECGs will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>45 msec from baseline or ≥500 msec), a single ECG will be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If the QTcF value remains above the threshold value (>45 msec from the average of the 3 predose values on Day 1 or ≥500 msec) on repeated measurement or is noted on >2 occasions with no identified alternative etiology for the increased QTcF, then discontinuation from study drug treatment may be required after discussion with the medical monitor.

Subjects in whom treatment is discontinued for increased QTc should have their QTc monitored closely until it normalizes or returns to baseline.

11.6.5 Ophthalmologic Examination

All pediatric subjects <18 years of age will undergo an ophthalmologic examination at the Screening Visit. Pediatric subjects <18 years of age at the Screening Visit who complete the Day 84 Visit will have an ophthalmologic examination that is to occur between the Day 84 Visit and the Safety Follow-up Telephone Contact. Pediatric subjects who discontinue from study drug treatment will have an ophthalmologic examination that is to occur between their last dose of study drug and completion of either the ETT Visit or the Safety Follow-up Visit.

The ophthalmologic examination includes

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

These examinations must be conducted by a licensed ophthalmologist or optometrist. The screening ophthalmologic examination must be completed and the results reviewed before enrollment. The Screening Visit ophthalmologic examination does not need to be repeated if there is documentation of an examination that met protocol criteria, and that it was conducted within 3 months before the Screening Period, or if there is documentation of bilateral lens removal.

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

- 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

If a clinically significant lens opacity or cataract is identified at Screening, the medical monitor must be notified. Additional ophthalmologic examinations may be required if a lens opacity or cataract is identified at Screening. The medical monitor should be notified of any additional ophthalmologic examinations.

11.6.6 Spirometry

Refer to Section 11.5.1 for the spirometry assessment.

11.6.7 Contraception and Pregnancy

The effects of VX-371 on conception, pregnancy, and lactation in humans are not known.

The effects of lumacaftor/ivacaftor on conception, pregnancy, and lactation in humans are not known. Neither lumacaftor nor ivacaftor showed any genotoxic potential in a standard battery of in vitro (Ames, Chinese hamster ovary cell chromosomal aberration) and in vivo (mouse micronucleus) studies. Lumacaftor and ivacaftor were each found to be non-teratogenic in reproductive toxicology studies in rats and rabbits (see the lumacaftor/ivacaftor Investigator's Brochure). However, a metabolite of lumacaftor, M28-lumacaftor, given to pregnant rats at very high levels far beyond levels observed in humans (>100-fold) produced fetal malformations. The significance of this finding in humans is unclear, but is highly unlikely to be of any clinical significance. Subjects should follow the contraception requirements outlined in this study protocol. The effects of lumacaftor/ivacaftor on the PK of hormonal contraceptives are not known; however, since lumacaftor is an inducer of CYP3A, it may reduce the effectiveness of hormonal contraceptives.

11.6.7.1 Contraception

Participation in this study requires a commitment from the subject and his/her partner to use at least 1 acceptable method of contraception, which much be used correctly with every act of sexual intercourse. Methods of contraception should be in successful use from at least 14 days before the first dose of study drug (unless otherwise noted) and until 90 days following the last dose of study drug.

Contraception for the couple is waived for the following:

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

- If the male is infertile (e.g., bilateral orchiectomy). Infertility may be documented through examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound before the first dose of the study drug.
- If the female is of non-childbearing potential, per the following:
  - Documented hysterectomy or a bilateral oophorectomy/salpingo-oophorectomy.
  - Postmenopausal: continuous amenorrhea for at least 12 months and serum FSH levels ≥40 mIU/mL.
  - Has not achieved menarche (has not had her first menstrual period). If a female achieves menarche during the study, she will need to follow acceptable methods of contraception or abstinence.

For subjects for whom contraception methods are not waived due to one of the reasons cited above, the following are acceptable contraceptive methods:

Table 11-4 Acceptable Methods of Contraception

Male subjects and their female (non-study) partners	• Male vasectomy 6 months or more previously, with a negative post-vasectomy semen analysis for sperm • Male or female condom with or without spermicide (either as a single product if commercially available and/or allowed according to local regulations; otherwise condom and spermicide as separate products) • Female bilateral tubal ligation performed at least 6 months previously • Female diaphragm, cervical cap, or vaginal sponge, each with spermicide (where available). • Female continuous use of an intrauterine device (non-hormone releasing or hormone releasing) for at least 90 days • Female combined (estrogen and progestogen-containing) or progestogen-only hormonal contraception associated with inhibition of ovulation if successfully used for at least 60 days
Female subjects and their male (non-study) partners[a]	• Male vasectomy 6 months or more previously, with a negative post-vasectomy semen analysis for sperm • Male or female condom with or without spermicide (either as a single product if commercially available and/or allowed according to local regulations; otherwise condom and spermicide as separate products) • Female bilateral tubal ligation performed at least 6 months previously • Female diaphragm, cervical cap, or vaginal sponge, each with spermicide (where available). • Female continuous use of an intrauterine device (non-hormone releasing) for at least 90 days

[a] Hormonal contraceptives are not considered an acceptable method in female study subjects because of the potential for a drug-drug interaction with lumacaftor/ivacaftor resulting in reduced exposure and contraception failure; however, female subjects are not required to discontinue their use of hormonal contraceptives as long as they agree to use an acceptable method of contraception as described above.

Important notes:

- Hormonal contraceptives are not considered an acceptable method in female study subjects because of the potential for a drug-drug interaction with lumacaftor/ivacaftor resulting in reduced exposure and contraception failure; however, female subjects are not required to

discontinue their use of hormonal contraceptives as long as they agree to use an acceptable method of contraception as described in Table 11-4.

- Local requirements may prohibit the use of some of these acceptable methods listed above. Please contact the medical monitor with any questions.
- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.
- Male and female subjects who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active.
- Female condom used with male condom (as a double method of contraception) is not an acceptable method of contraception due to risk of tearing; a different acceptable method of birth control must be used as described in Table 11-4.
- Male subjects must not donate sperm after the first dose of study drug, throughout the study, and for 90 days following the last dose of study drug.
- Female subjects and female partners of male subjects should not plan to become pregnant during the study through 90 days following the last dose of study drug.
- Female subjects should not nurse a child from the start of study drug dosing through 90 days following the last dose of study drug.

Unique situations that may not fall within the above specifications may be discussed with the medical monitor on an individual basis.

11.6.7.2 Pregnancy

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

If a subject or the female partner of a male subject becomes pregnant while participating in the study, study drug must be permanently discontinued immediately. The investigator must notify the medical monitor and Vertex GPS within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form.

The subject or partner will be followed until the end of the pregnancy and the infant will be followed for 1 year after the birth, provided informed consent is obtained. A separate ICF (and assent form, if applicable) will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

12 STATISTICAL AND ANALYTICAL PLANS

This section presents a summary of the planned analyses for this protocol. Statistical analysis details will be provided in the Statistical Analysis Plan (SAP), and clinical pharmacologic analysis details will be provided in the Clinical Pharmacology Analysis Plan (CPAP), both of which will be finalized before the clinical database lock for the study and treatment unblinding.

12.1 Sample Size and Power

The primary efficacy endpoint is the absolute change in ppFEV$_1$ from study baseline to the Day 28 measurements in each Treatment Period.

The null hypothesis to be tested is that the mean change from study baseline in $ppFEV_1$ to the Day 28 measurements is the same for VX-371 in combination with HS versus HS alone.

To have a feasible sample size and study duration, this study uses a crossover design. Assuming a standard deviation (SD) of 7 percentage points, 50 subjects per sequence are needed to have an approximately 81% power to detect a 3 percentage point treatment difference in the mean absolute change in $ppFEV_1$ from study baseline at Day 28 between VX-371 + HS and HS alone. The study will have an approximately 80% power to detect a 3 percentage point (within treatment) change from baseline at Day 28 in $ppFEV_1$ for VX-371. A 2-sided significance level of 0.05 was used in the sample size calculations. The sample size also takes into consideration an assumed dropout rate of 10%.

12.2 Analysis Sets

The All Subjects Set is defined as all subjects who were randomized or have received at least 1 dose of inhaled study drug (i.e., all subjects in the study). All subject data listings will be referenced using the All Subjects Set, unless otherwise specified.

The Full Analysis Set (FAS) is defined as all randomized subjects who carry the intended homozygous *F508del-CFTR* mutation and have received at least 1 dose of inhaled study drug. The FAS is to be used in efficacy analyses in which subjects will be analyzed according to the treatment sequence to which they were randomized. All analyses of background data and efficacy data will be based on the FAS.

The Safety Set is defined as all subjects who received at least 1 dose of inhaled study drug. All analyses of safety data will be based on the Safety Set. Subjects will be analyzed according to the treatment sequence received.

12.3 Statistical Analysis

The primary objective of this study is to evaluate the safety and efficacy of treatment with VX-371 in HS compared to HS alone treatment in subjects with CF who are homozygous for the *F508del-CFTR* mutation and being treated with Orkambi.

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).

Statistical analysis and presentation details will be provided in the SAP for the study.

12.3.1 General Considerations

All individual subject data for those randomized or exposed to inhaled study drug will be presented in data listings.

Continuous variables will be summarized using the following descriptive summary statistics: number of subjects (n), mean, SD, standard error (SE), median, minimum value (min), and maximum value (max). The precision of the measurement for each continuous variable will be specified in the SAP.

Categorical variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place.

Treatment emergent (TE) period for Treatment Period 1 will correspond to data from the first dose of inhaled study drug in the first period to the safety evaluation visit (28 days after the last dose in the first period and prior to the first dose of Treatment Period 2). Similarly, the TE period for Treatment Period 2 will correspond to data from the first dose of inhaled study drug in Treatment Period 2 through the Safety Follow-up Telephone Contact, or 28 days after the last dose in the second period for subjects who do not have a Safety Follow-up Telephone Contact.

Baseline: For this crossover study, 2 types of baseline will be defined. The **study baseline** is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of inhaled study drug in the study. Study baseline will be used for all summaries of demographics, background, and baseline characteristics as well as all efficacy data analyses, including the primary endpoint analysis. In addition, **period baseline** is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of inhaled study drug in each treatment period. For Treatment Period 2, the baseline value should be from an assessment measured after the TE period for Treatment Period 1. Period baseline will be used for all safety data analyses. For ECG, baseline for Period 1 will be defined as the average of the 3 pretreatment measurements on Day 1.

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

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

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. Additionally, all subject data will be presented in subject data listings. All summaries will be based on the FAS unless otherwise specified in the SAP for the study. No statistical hypothesis testing will be performed on background characteristics.

12.3.2.1 Subject Disposition

The number and percentage of subjects in the FAS will be summarized by treatment sequence in each of the following disposition categories:

- Completed inhaled study drug treatment
- Prematurely discontinued treatment and the reasons for discontinuation
- Last scheduled on-treatment visit completed for subjects who discontinued treatment
- Completed study
- Prematurely discontinued the study and the reasons for discontinuation
- Last scheduled visit completed

12.3.2.2 Demographics, Medical History, and Baseline Characteristics

Demographic, medical history, and baseline characteristics will be summarized by treatment sequence. Protocol deviations will be provided as a subject data listing only. Important protocol deviations will be summarized.

The following demographics and study baseline characteristics will be summarized by treatment sequence for the FAS: sex, race, ethnicity, age, weight, height, BMI, region, study baseline $ppFEV_1$, [redacted].

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 categorized as follows:

- **Prior medication:** any medication that started before the first dose of inhaled study drug, regardless of when it ended.
- **Concomitant medication:** medication continued or newly received during the TE period for Treatment Period 1 or Treatment Period 2.

A given medication can be classified as a prior medication, a concomitant medication, or both prior and concomitant. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether the medication was taken before initial dosing or concomitantly, it will be considered as prior and concomitant.

Prior medications will be summarized by treatment sequence, and concomitant medications will be summarized by treatment based on the FAS.

12.3.2.4 Study Drug Exposure and Compliance

Exposure to study drug (i.e., duration of treatment) will be summarized by treatment for the FAS in terms of duration of treatment a subject received (in days), defined as the last day minus the first day of study drug plus 1 within the Treatment Period.

Study drug compliance will be calculated as follows:

$$100 \times [1 - (\text{Total number of days study drug interrupted}) / (\text{Duration of study drug exposure})]$$

The total number of days of study drug interrupted is defined as the sum of (number of days of study drug interrupted in each interruption interval); where number of days of study drug interrupted in each interval is defined as the interruption end date – the corresponding interruption start date + 1.

Duration of treatment and study drug compliance will be summarized by means of descriptive summary statistics.

12.3.3 Efficacy Analysis

The primary efficacy objective of this study is to evaluate the efficacy of VX-371 plus HS versus HS alone. For efficacy analysis, the statistical inference will be based on change from study baseline.

12.3.3.1 Analysis of Primary Efficacy Variables

The primary efficacy endpoint is the absolute change in $ppFEV_1$ from study baseline at Day 28 in each Treatment Period.

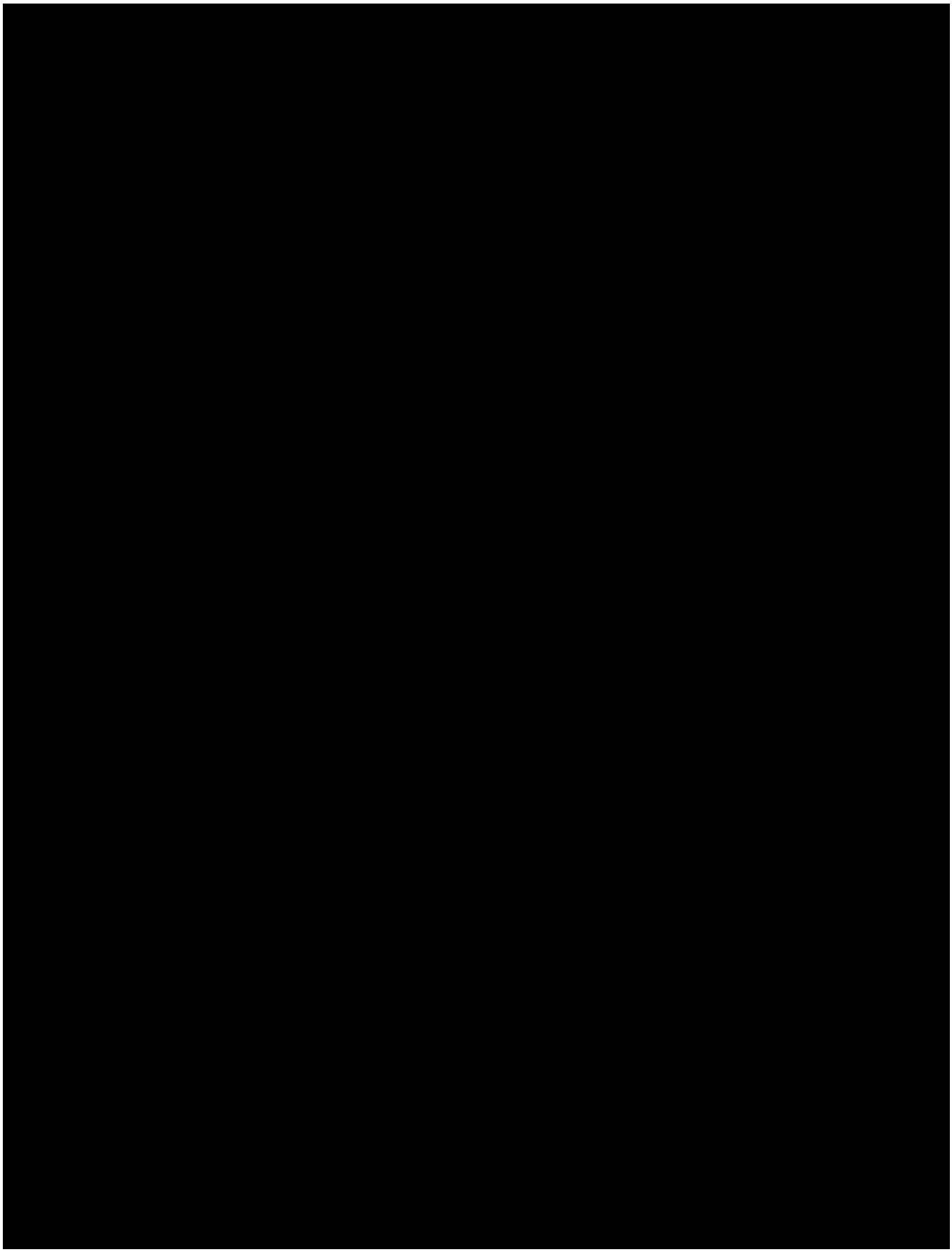
The null hypothesis to be tested is that the mean change from study baseline in $ppFEV_1$ at Day 28 is the same for VX-371 with HS versus HS alone.

The primary efficacy analysis is based on a mixed-effects model. This model will include the absolute change from study baseline in $ppFEV_1$ at Day 28 as the dependent variable, study

baseline for $ppFEV_1$, treatment, and period as fixed effects, and subject nested within sequence as a random effect. The within-subject covariance will be assumed to have the compound symmetry structure. Denominator degrees of freedom for the F-test for fixed effects will be estimated using the Kenward-Roger approximation.[42] No imputation of missing data will be done. Assuming that the subjects have dropped out at random, an estimate of treatment effect will be based on such subjects and will then be combined with the estimate from subjects who have data in both treatment periods with weights based on the precision of these estimates.

The estimated mean of the dependent variable, a 95% CI, and a 2-sided *P* value will be provided for each treatment. Similarly, the estimated between treatment differences along with the corresponding 95% CI and 2-sided *P* values will be presented. Additionally, a mixed model of repeated measures (MMRM) will be used with period, study baseline for $ppFEV_1$, visit, treatment, and treatment by visit, study baseline for $ppFEV_1$ by visit, as fixed effects and subject nested within sequence as a random effect. The absolute change from study baseline in $ppFEV_1$ will be the dependent variable. The repeated measures analysis will enable use of all post-baseline available data and provide least square means estimates at each visit within a given treatment as well as estimates of treatment difference at each visit or across all visits.

[redacted]



[redacted]

[redacted]

12.3.4 Safety Analysis

All safety analyses will be based on the set of data associated with the TE period for Treatment Period 1 and the TE period for Treatment Period 2. Safety analyses will be based on the Safety Set. The summaries will be by treatment received.

For safety analysis, the period baseline will be used.

All safety data will be presented in individual subject data listings.

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

- Incidence of treatment-emergent adverse event (TEAEs)
- Clinical laboratory values (i.e., hematology, serum and plasma chemistry, coagulation studies, and urine studies)
- ECG results
- Vital signs
- Ophthalmologic examination results (for pediatric subjects <18 years of age only)
- Spirometry

12.3.4.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs or TEAEs, defined as follows:

Pre-treatment AEs are defined as AEs that started before the start of inhaled study drug dosing.

TEAE: any AE that increased in severity or that was newly developed during the TE period for Treatment Period 1 or Treatment Period 2. An AE that starts (or increases in severity) during a specific Treatment Period will be attributed to the inhaled study drug the subject was receiving during the Treatment Period.

For AEs with missing or partial start date, if there is no clear evidence that the AEs started (or increased in severity) before the first dose, the start date will be imputed to the first dosing date and the AE assigned to the treatment in Treatment Period 1.

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

- All TEAEs
- TEAEs by relationship
- TEAEs by maximal severity
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- TEAEs leading to death

- Frequently reported TEAEs

Summaries will be presented by MedDRA system organ class and preferred term using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once, only the maximum severity level will be presented in the severity summaries, and the worst/highest relationship level in the relationship summaries. An AE overview table will be provided. In addition, a listing containing individual subject AE data for all deaths and other serious and significant AEs will be provided separately. All AEs, including pre-treatment AEs, will be presented in individual subject data listings.

12.3.4.2 Clinical Laboratory Assessments

The raw values and change from period baseline values of the continuous laboratory parameters will be summarized in SI units by treatment group at each scheduled time point during the TE period.

The number and percentage of subjects with at least 1 potentially clinically significant (PCS) event during the TE period will be summarized by treatment group. The PCS criteria and the parameter selection criteria will be provided in the SAP.

Results of urinalysis and serum pregnancy test will be listed in individual subject data listings only. In addition, a listing containing individual subject laboratory measurements outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

Urine sodium to potassium ratios will be summarized by treatment group.

Clinically significant abnormal laboratory findings will be reported as AEs.

12.3.4.3 Electrocardiogram

A summary of raw values and change from period baseline values will be provided by dose group at each scheduled visit for the following ECG measurements: heart rate, PR, QT, QRS, and QTcF intervals. In addition, the number and percentage of subjects by maximum on-treatment value of QTcF intervals, categorized as ≤450 msec, >450 msec and ≤480 msec, >480 msec and ≤500 msec, and >500 msec, as well as maximum on-treatment change from baseline value of QTcF intervals, categorized as ≤30 msec, >30 msec and ≤60 msec, and >60 msec, will be provided. Clinically significant abnormal findings will be reported as AEs.

12.3.4.4 Vital Signs

The following vital signs will be summarized by treatment group at each scheduled time point: systolic and diastolic blood pressure (mmHg), body temperature, pulse rate (beats per minute), and respiratory rate (breaths per minute). Clinically significant abnormal findings will be reported as AEs.

12.3.4.5 Physical Examination

Physical examination results will be presented in individual subject data listings only. Clinically significant results identified after screening will be reported as AEs.

12.3.4.6 Ophthalmologic Examinations

The ophthalmologic exams for pediatric subjects <18 years of age will be presented as by-subject listings.

12.3.4.7 Spirometry

Spirometry data will be summarized based on the Safety Set. This will include the number and percentage of subjects at each visit with predefined decreases in FEV_1 relative to baseline on pre- and postdose spirometry.

12.3.4.8 Other Safety Analysis

Not applicable

12.3.5 Interim and IDMC Analyses

12.3.5.1 Interim Analysis

Not applicable

12.3.5.2 IDMC Analysis

The IDMC's objectives and operational details will be defined in a separate document (IDMC charter). The IDMC will conduct regular planned safety reviews of study data as outlined in the IDMC charter.

12.4 Clinical Pharmacology Analysis

12.4.1 Pharmacokinetic Analysis

The PK Analysis Set will be used for all PK analyses.

Urine concentrations of VX-371 and plasma concentrations of VX-371, [redacted] will be summarized using descriptive statistics by collection time and treatment group. Further details of the planned PK analysis will be provided in the CPAP. Any deviation from the reporting and analysis plan will be reported in the clinical study report.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

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

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

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

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

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

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time 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 inhaled study drug, or
  - the ETT Visit, if that visit is 28 days or later following the last dose of inhaled study drug (see Section 8.1.4).

All subjects will be queried, using nonleading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms will be identified as 1 overall event or diagnosis. All AEs for enrolled subjects will be recorded in the 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 nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed August 2015). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." In considering the severity of an AE in a pediatric subject, the investigator will consider that reference ranges for pediatric clinical laboratory parameters may differ from those given in the CTCAE. The severity of an AE that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

Classification	Definition
Mild (Grade 1)	Mild level of discomfort and does not interfere with regular activities
Moderate (Grade 2)	Moderate level of discomfort and significantly interferes with regular activities
Severe (Grade 3)	Significant level of discomfort and prevents regular activities
Life-threatening (Grade 4)	Any adverse drug 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 reappeared on re-exposure to the investigational study drug.
Possibly related	There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
Unlikely related	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
Not related	The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the study subject's medical record).

13.1.1.6 Study Drug Action Taken

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

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

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

13.1.1.7 Adverse Event Outcome

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

Table 13-4 Classifications for Outcome of an AE

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

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

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

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation in the study and is suspected of being a delayed toxicity due to administration of the study drugs)

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

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

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

13.1.2.2 Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through the Safety Follow-up Telephone Contact, regardless of causality, will be reported by the investigator to Vertex GPS **within 24 hours**. In addition, all SAEs that occur after the Safety Follow-up Telephone Contact 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 SAE Form, relationship to study drug(s) will be assessed only as related (includes possibly related) or not related (includes unlikely related), and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report to Vertex the outcome of the event using the SAE Form.

13.1.2.3 Reporting Serious Adverse Events

The investigator is responsible for notifying the sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. The SAE Form will be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (Preferred Choice)

Fax: [redacted]

Contact Telephone: [redacted]

13.1.2.4 Expedited Reporting and Investigator Safety Letters

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

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

13.1.3 Adverse Device Effects

13.1.3.1 Definition of an Adverse Device Effect

An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This includes any AE resulting from insufficiencies or inadequacies in the Instructions For Use, the deployment, the installation, the operation, or any malfunction of the investigational medical device. This includes any event that is a result of a user error or intentional misuse.

13.1.3.2 Definition of Serious Adverse Device Effect

A serious adverse device effect (SADE) is an ADE that:

- Led to a death.
- Led to a serious deterioration in health that
  - resulted in a life-threatening illness or injury, or
  - resulted in an injury or permanent impairment of a body structure or a body function, or
  - required in-subject hospitalization or prolongation of existing hospitalization, or
  - resulted in medical or surgical intervention to prevent life-threatening illness.
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

13.1.3.3 Reporting Adverse Device Effects

All ADEs, including SADEs, that occur after obtaining informed consent and assent (where applicable), and before the return of the device by the subject, must be reported to Vertex GPS within 24 hours of identification.

The Adverse Device Effect Form will be completed for new/initial reports as well as to report follow-up information on previously reported ADEs. Investigators are asked to report follow-up information as soon as it becomes available.

Please send completed Adverse Device Effect Form to Vertex GPS via:

Email: [redacted] (Preferred Choice)

Fax: [redacted]

Contact Telephone: [redacted]

By definition, an ADE is also an AE and the investigator should also follow the documentation procedures outlined in Section 13.1.1.3. If the AE is also an SAE, the investigator will separately document and report the SAE (see Section 13.1.2.2).

13.1.3.4 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for evaluating and reporting unanticipated adverse device effects (UADEs) involving the investigational device used in this study 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 IECs, as applicable.

It is the responsibility of the investigator or designee to report all UADEs to their local IRB/local IEC, as applicable.

13.2 Administrative Requirements

13.2.1 Ethical Considerations

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

13.2.2 Subject Information and Informed Consent

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

13.2.3 Investigator Compliance

No modifications to the protocol will be made without the approval of both the investigator and Vertex. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (i.e., efficacy assessments) will require IRB/IEC notification

before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. Vertex will submit all protocol modifications to the required regulatory authorities.

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

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

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

13.2.6 Record Retention

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

13.2.7 Study Termination

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

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

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

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

13.3 Data Quality Assurance

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

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each screened 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 whom they are responsible.

A CRF will be completed for each randomized 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.

13.6 Publications and Clinical Study Report

[redacted]

13.6.2 Clinical Study Report

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

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX15-371-101	Version #: 3.0	Version Date 22 July 2016
Study Title: A Phase 2a, Randomized, Double-blind, Placebo-controlled, Incomplete Block, Crossover Study to Evaluate the Safety and Efficacy of VX-371 in Subjects Aged 12 Years or Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation, and Being Treated With Orkambi		

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

[redacted]

15.2 Investigator Signature Page

Protocol #: VX15-371-101	Version #: 3.0	Version Date 22 July 2016
Study Title: A Phase 2a, Randomized, Double-blind, Placebo-controlled, Incomplete Block, Crossover Study to Evaluate the Safety and Efficacy of VX-371 in Subjects Aged 12 Years or Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation, and Being Treated With Orkambi		

I have read Protocol VX15-371-101, Version 3.0 and agree to conduct the study according to its terms. I understand that all information concerning VX-371 and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date