1 TITLE PAGE

PARION SCIENCES INCORPORATED

Clinical Study Protocol

CLEAN-PCD
Clearing Lungs with ENaC Inhibition in Primary Ciliary Dyskinesia

A Phase 2a, 2-part, Randomized, Double-blind, Placebo-controlled, Incomplete Block Crossover Study to Evaluate the Safety and Efficacy of VX-371 Solution for Inhalation With and Without Oral Ivacaftor in Subjects With Primary Ciliary Dyskinesia

Parion Sciences Study Number: PS-G202

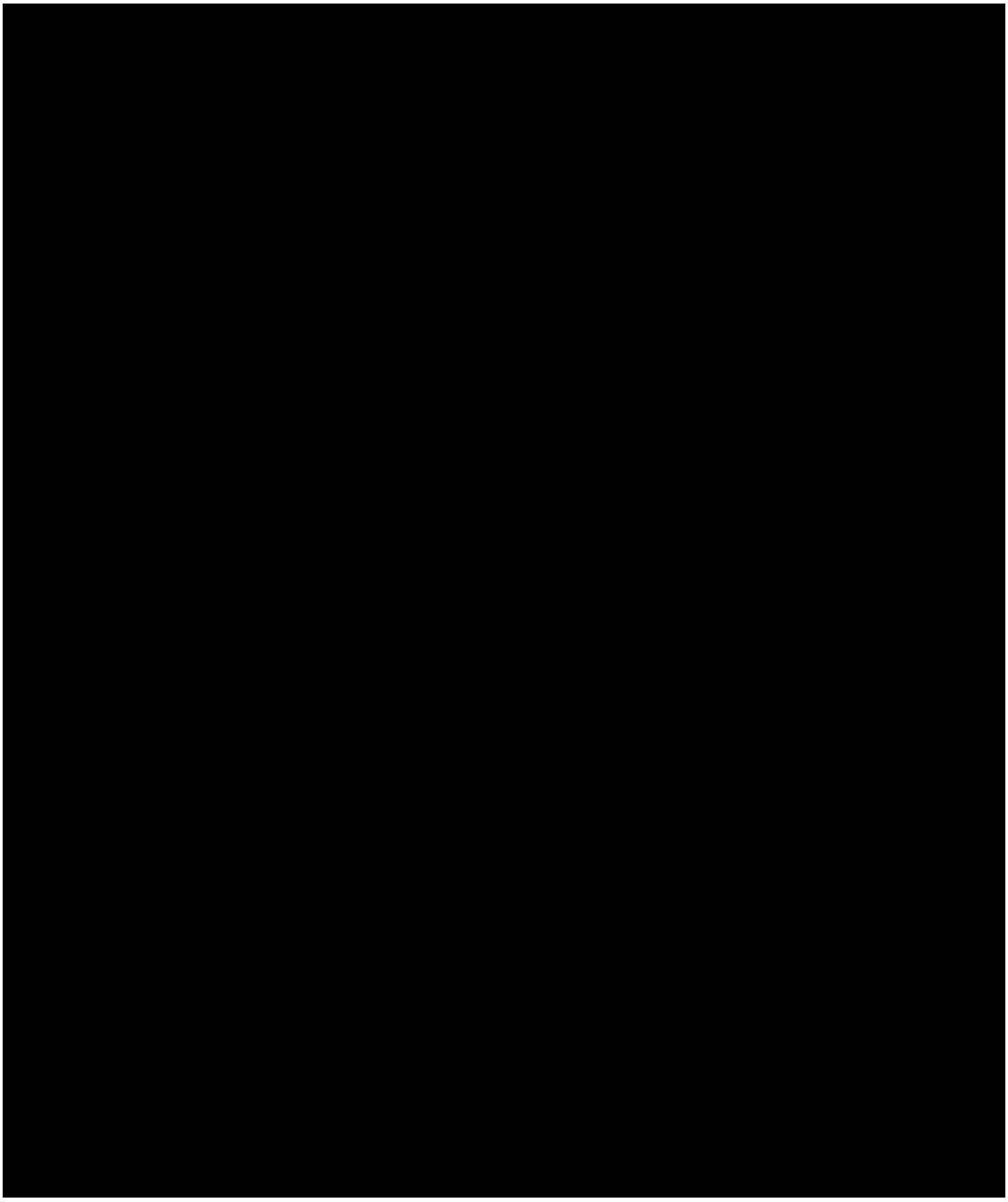
IND Number: [redacted]

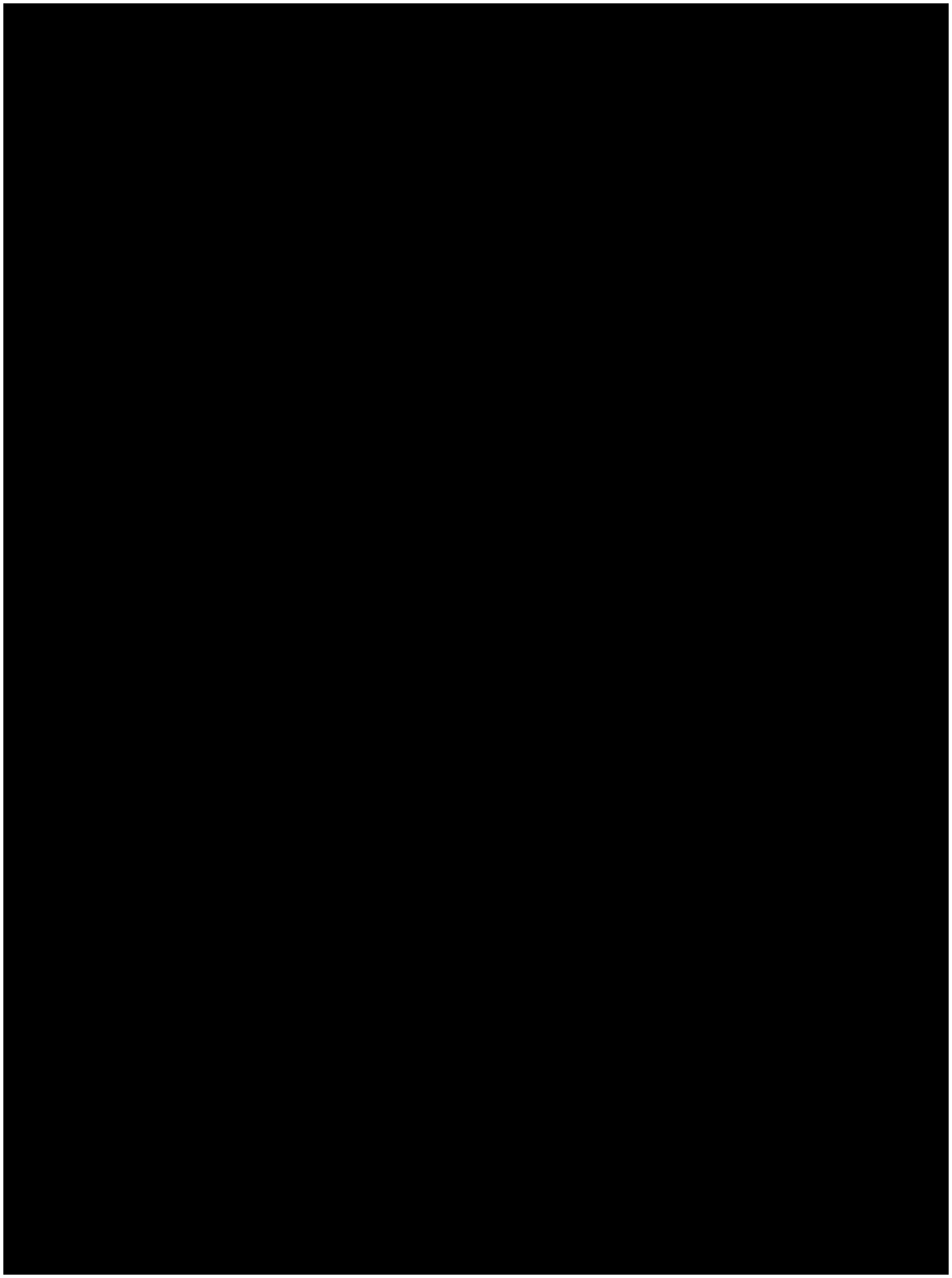
EudraCT Number: 2015-004917-26

Date of Protocol: 31 October 2016 (Version 6.0)

Parion Sciences, Incorporated
2800 Meridian Parkway, Suite 195
Durham, NC USA 27713

[redacted]





2 PROTOCOL SYNOPSIS

Title A Phase 2a, 2-part, Randomized, Double-blind, Placebo-controlled, Incomplete Block Crossover Study to Evaluate the Safety and Efficacy of VX-371 Solution for Inhalation With and Without Oral Ivacaftor in Subjects With Primary Ciliary Dyskinesia

Brief Title CLEAN-PCD: Clearing Lungs with ENaC Inhibition in Primary Ciliary Dyskinesia

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

Objectives

Part A Objectives

Primary

To evaluate the safety and efficacy of treatment with VX-371, administered with and without 4.2% hypertonic saline (HS) in subjects with primary ciliary dyskinesia (PCD) who are ≥12 years of age

Secondary

To evaluate the effect of VX-371, administered with and without 4.2% HS, on quality of life (QOL) in subjects with PCD who are ≥12 years of age

Part B Objectives

Primary

To evaluate the safety and efficacy of treatment with ivacaftor and VX-371, administered with and without 4.2% HS in subjects with PCD who are ≥12 years of age

Secondary

To evaluate the effect of ivacaftor and VX-371, administered with and without 4.2% HS on QOL in subjects with PCD who are ≥12 years of age

Endpoints

Part A Endpoints

Primary

- Results of safety and tolerability assessments of adverse events (AEs), clinical laboratory values (urine, serum and plasma chemistry, and hematology), 12-lead electrocardiograms (ECGs), spirometry, vital signs, and pulse oximetry
- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from study baseline, after 28 days of treatment in Part A

Secondary

- Change in QOL score as measured by the Quality of Life-PCD Questionnaire (QOL-PCD) and the St. George's Respiratory Questionnaire (SGRQ) from study baseline, after 28 days of treatment in Part A

[redacted]

[redacted]

Part B Endpoints

Primary

- Results of safety and tolerability assessments of AEs, clinical laboratory values (urine, serum and plasma chemistry, and hematology), 12-lead ECGs, spirometry, vital signs, and pulse oximetry
- Absolute change in $ppFEV_1$ from study baseline and Part B baseline, after 28 days of treatment in Part B

Secondary

- Change in QOL score as measured by the QOL-PCD and SGRQ from study baseline and Part B baseline, after 28 days of treatment in Part B

[redacted]

Number of Subjects

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

Study Population

Male and female subjects ≥12 years of age with a confirmed diagnosis of PCD

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, oral nebulized inhalation

Active substance: VX-371 in HS

Activity: ENaC inhibitor + osmolyte

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: ivacaftor

Activity: cystic fibrosis transmembrane regulator (CFTR) potentiator

Strength and Route of Administration: 150-mg tablet, oral

Study Duration

Part A Study Duration

Excluding the Screening Period, the planned study duration is 113 days from Day 1 to Safety Follow-up Telephone Call, approximately 28 days after the last dose of study drug.

Part A + Part B Study Duration

Excluding the Screening Period, the planned study duration is 141 days from Day 1 to Safety Follow-up Telephone Call, approximately 28 days after the last dose of study drug.

Study Design

Phase 2a, 2-part, randomized, double-blind, placebo-controlled, incomplete block crossover, multicenter study in subjects ≥12 years of age with PCD.

Subjects will be randomized to 1 of 4 treatment sequences as shown in Table 2-1.

Table 2-1 Study PS-G202 Treatment Sequences

	Part A		Part B
Sequence	Treatment Period 1	Treatment Period 2	Treatment Period 3
1	VX-371 in 4.2% HS	4.2% HS	4.2% HS + ivacaftor
2	4.2% HS	VX-371 in 4.2% HS	VX-371 in 4.2% HS + ivacaftor
3	VX-371 in 0.17% saline	Placebo (0.17% saline)	Placebo (0.17% saline) + ivacaftor
4	Placebo (0.17% saline)	VX-371 in 0.17% saline	VX-371 in 0.17% saline + ivacaftor

This study includes the following:

- **Screening Period:** Day of Screening Visit until Day 1 (first dose of study drug). The Screening Visit can occur Day -38 to Day -5, relative to the first dose of study drug.
- **Treatment Periods:**
  - **Part A:**
    - Treatment Period 1: Day 1 (first dose of study drug) through Day 29 (28 days of treatment)
    - Washout Period: Day 29 through Day 56 (28 days)
    - Treatment Period 2: Day 57 through Day 85 (28 days of treatment)
  - **Part B (Optional):**
    - Treatment Period 3: Day 85 (first dose of oral ivacaftor) through Day 113 (28 days of treatment)
      Note: There is no Washout Period between the last dose of study drug in Part A and the first dose of study drug in Part B.
- **Safety Follow-up Period**: 28 days (± 7 days) after the last dose of study drug

If the subject prematurely discontinues study drug, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the subject decides to terminate study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Telephone Call approximately 28 days (± 7 days) after their last dose of study drug.

Assessments

Efficacy: spirometry, QOL-PCD, SGRQ

Safety: AEs, spirometry, clinical laboratory values (urine, serum and plasma chemistry, and hematology), ECGs, vital signs, and pulse oximetry

[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.

Part A

The primary efficacy objective of Part A is to evaluate the efficacy of VX-371 with and without HS in subjects ≥12 years of age with PCD. For the Part A efficacy analysis, statistical inferences will be based on change from study baseline, and formal comparisons will be made between groups. The null hypotheses to be tested in Part A are that the absolute absolute change from study baseline in $ppFEV_1$ after 28 days of treatment is the same for 1) VX-371 in HS versus placebo; 2) VX-371 versus placebo; and 3) VX-371 in HS versus HS alone.

To have a feasible sample size and study duration, Part A of this study uses a crossover design. Assuming a standard deviation of 7 percentage points, 50 subjects each for Treatment Sequence 1 and 2 are needed to have approximately 81% power to detect a 3-percentage point treatment difference in the mean absolute change in $ppFEV_1$ from study baseline, after 28 days of treatment between VX-371 + HS and HS alone. Part A of the study will have approximately 87% power to detect a 4-percentage point change from baseline, after 28 days of treatment in $ppFEV_1$ between VX-371 + HS and placebo. The power to detect a 3 percentage point difference between VX-371 and placebo is about 51%. The sample size estimate was based on 10000 simulation runs with an incomplete block design assuming no dropouts. In the simulation, the correlation between responses to the 2 treatments within a subject was assumed to be 0. Furthermore, a 2-sided significance level of 0.05 was used in the sample size determination with no multiplicity adjustment. 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, after 28 days of treatment in each Treatment Period of Part A. The primary efficacy analysis is based on a mixed-effects model. This model will include the absolute change from study baseline in $ppFEV_1$ after 28 days of treatment as the dependent variable, treatment and period as fixed effects, and subject as a random effect. The within-subject covariance will be assumed to have the compound symmetry (CS) structure. Denominator degrees of freedom for the F-test for fixed effects will be estimated using the Kenward-Roger approximation.

The estimated mean of the dependent variable, a 95% confidence interval (CI), and a 2-sided *P* value will be provided for each treatment. There will be no adjustment for multiplicity. Similarly, the estimated between-treatment differences along with the corresponding 95% CI and 2-sided *P* values will be presented.

Part B

For the Part B primary efficacy endpoints, absolute change in $ppFEV_1$ from study baseline and Part B baseline, after 28 days of treatment, descriptive summary statistics (n, mean, SD, SE, median, minimum, and maximum), and within-group comparisons will be made.

The within-group *P* value and the 95% CI based on normal approximation will be provided for absolute change in $ppFEV_1$:

- From study baseline, after 28 days of treatment in Part B
- From Part B baseline, after 28 days of treatment in Part B

IDMC Reviews

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

3 SCHEDULE OF ASSESSMENTS

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

Table 3-1 Study PS-G202: Screening Period

Event/Assessment	Screening Period (Day -38 to Day -5)
Clinic visit	X
Informed consent/assent	X
Inclusion/exclusion criteria review[a]	X
Demographics	X
Medical history	X
Medications review	X
Height and weight[b]	X
Pulse oximetry and vital signs[c]	X
Full physical examination[d]	X
12-lead ECG[e]	X
Spirometry[f]	X
Single dose of HS to assess tolerability	X
Serum β-HCG[g]	X
Serum FSH[h]	X
Serum chemistry	X
Plasma chemistry[i]	X
Hematology	X
PCD genotype[j]	X
Urinalysis	X
Adverse events and serious adverse events	Continuous from signing of ICF/assent (if applicable) and initiation of study procedures through the Safety Follow-Up Telephone Call

[a] After obtaining informed consent/assent, inclusion criteria # 4A and # 4B (Section 9.1), as applicable, must be confirmed prior to initiating any other screening assessments during the Screening Period.
[b] Height and weight will be measured with shoes off. BMI will be calculated.
[c] Pulse oximetry and vital signs will be performed after the subject has been seated or supine for at least 5 minutes.
[d] Physical examination of all body systems, excluding rectal and genitourinary examinations.
[e] The ECG will be performed after the subject has been seated or supine for at least 5 minutes. Prior to placing ECG leads, the record will be reviewed for the presence of dextrocardia. Subjects with dextrocardia will have all ECG limb and chest (V) leads reversed.
[f] The spirometry assessment will be performed within 60 minutes before the test dose of HS and 60 minutes (± 5 minutes) after the test dose of HS. See Section 8.1.1 for more information.
[g] A serum 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] Plasma potassium.
[j] Unless a confirmed PCD genotype is an inclusion criterion for a particular subject (see Section 9.1), the genotype result is not required in order for randomization to occur.

Table 3-2 Study PS-G202: Treatment Period

	Part A						Part B								
	Treatment Period 1 (Day 1 through Day 29)						Treatment Period 2 (Day 57 through Day 85)					Treatment Period 3[a] (Day 85 through Day 113)				
Event/Assessment	Day 1	Day 4 Telephone Call (±1 Day)	Day 15[b] Telephone Call (±1 Day)	Day 15[b] Visit (±3 Days)	Day 29 Visit (±3 Days)	Washout Day 29 to Day 56 (+3 Days)	Day 57 Visit	Day 60 Telephone Call (±1 Day)	Day 71[b] Telephone Call (±1 Day)	Day 71[b] Visit (±3 Days)	Day 85[c] Visit (±3 Days)	Day 86 Telephone Call	Day 87 Telephone Call	Day 99[b,d] Telephone Call (-11 Days)	Day 99[b,d] Visit (-11 Days)	Day 113 Visit (±3 Days)
Pre-visit reminder contact[e]	X				X		X				X					X
Part B informed consent/assent							X[f]									
Clinic visit	X			X	X		X			X	X				X	X
Safety telephone call[g]		X	X					X	X			X	X	X		
Inclusion/exclusion criteria review	X															
Randomization[h]	X															
Medical history	X															
QOL-PCD[i]	X				X		X				X					X
SGRQ[i]	X				X		X				X					X

[a] Subjects will sign a new ICF (or assent if applicable) before the Day 85 Visit in order to continue into Treatment Period 3. If the subject does not sign the new ICF, Treatment Period 2 will end at Day 85 and the subject will continue through to the Safety Follow-up Telephone Call.

[b] Day 15, Day 71, and Day 99 clinic visit required for subjects randomized prior to IDMC approval to change visit to a telephone call.

[c] At the Day 85 Visit, subjects will remain in clinic for a total of 2 to 4 hours after dosing with study drug. The duration of the extended time for each subject (2 to 4 hours) will be left up to the discretion of the investigator. Post-dose safety assessments will be done prior to discharge from the clinic.

[d] Day 99 Visit or telephone call may occur any time between Day 88 and Day 99. The clinic visit may be changed to a telephone call after approval from the IDMC.

[e] Pre-visit reminder should be done 1 day before the visit, via telephone call, email, or text message, to remind subject to withhold short-acting bronchodilators for 4 hours prior to spirometry assessment performed at each visit, to withhold long-acting bronchodilators the night before the visit, and to administer study drug at least 4 hours before visits on Day 29, Day 85, and Day 113.

[f] Subjects who participate in Part B will sign a new ICF for Treatment Period 3. This should occur at least 2 weeks prior to Day 85 to allow for delivery of study drug for Treatment Period 3.

[g] A safety telephone call will occur on Day 4, Day 15 (if no visit conducted), Day 60, Day 71 (if no visit conducted), Day 86, Day 87, and between Day 88 and Day 99 (if no Day 99 Visit conducted) for safety purposes (e.g., inquiry about adverse events). The telephone call on Day 86 and 87 will continue until the IDMC deems them unnecessary.

[h] Randomization will occur once it is confirmed that the subject meets all eligibility criteria, and approximately 5 to 10 days prior to Day 1, in order for study drug to be delivered to the site and in time for the first dosing.

[i] The QOL-PCD assessment must be completed before the start of any other assessments scheduled at this visit. The SGRQ should be completed immediately following the QOL-PCD assessment and before the start of other assessments.

Table 3-2 Study PS-G202: Treatment Period

	Part A											Part B				
	Treatment Period 1 (Day 1 through Day 29)						Treatment Period 2 (Day 57 through Day 85)					Treatment Period 3[a] (Day 85 through Day 113)				
Event/Assessment	Day 1	Day 4 Telephone Call (±1 Day)	Day 15[b] Telephone Call (±1 Day)	Day 15[b] Visit (±3 Days)	Day 29 Visit (±3 Days)	Washout Day 29 to Day 56 (+3 Days)	Day 57 Visit	Day 60 Telephone Call (±1 Day)	Day 71[b] Telephone Call (±1 Day)	Day 71[b] Visit (±3 Days)	Day 85[c] Visit (±3 Days)	Day 86 Telephone Call	Day 87 Telephone Call	Day 99[b,d] Telephone Call (-11 Days)	Day 99[b,d] Visit (-11 Days)	Day 113 Visit (±3 Days)
Medications review	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Concomitant treatments and procedures	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
[redacted]																
Pulse oximetry, chest auscultation, and vital signs[k]	X[l]			X	X		X[l]			X	X[l]				X	X
Height and weight[m]	X				X		X				X				X	X
Physical examination[n]	X			X	X		X			X	X				X	X
12-lead ECG[o]	X			X	X		X			X	X				X	X
Spirometry	X[p]			X	X		X[p]			X	X[p]				X	X

[redacted]

k Vital signs and pulse oximetry will be performed after the subject has been seated or supine for at least 5 minutes.

l Vital signs, chest auscultation, and pulse oximetry will be performed pre-dose and 1 hour post-dose of study drug in clinic at the Day 1 Visit and Day 57 Visit. At the Day 85 Visit, if the subject continues into Part B, vital signs, chest auscultation, and pulse oximetry will be performed pre-dose and post-dose prior to discharge from the clinic. If the subject does not continue into Part B, vital signs, chest auscultation, and pulse oximetry will only be performed once at the Day 85 Visit.

m Height and weight will be measured with shoes off. BMI will be calculated.

n Full physical examination of all body systems, excluding rectal and genitourinary examinations, on Day 1, Day 29, Day 57, Day 85, and Day 113. An abbreviated physical examination (HEENT, neck, chest auscultation, cardiovascular, and skin) at Day 15, Day 71, and Day 99, if the visits are planned.

o The ECG will be performed after the subject has been seated or supine for at least 5 minutes. Prior to placing ECG leads, the record will be reviewed for the presence of dextrocardia. Subjects with dextrocardia will have all ECG limb and chest (V) leads reversed.

p Spirometry will be performed prior to dosing with study drug and 1 hour post-dose at the Day 1 and Day 57 Visits. At the Day 85 Visit, if the subject continues into Part B, spirometry will be performed pre-dose and post-dose, prior to discharge from the clinic. If the subject does not continue into Part B, spirometry will only be performed once at the Day 85 Visit.

Table 3-2 Study PS-G202: Treatment Period

	Part A									Part B				
	Treatment Period 1 (Day 1 through Day 29)					Treatment Period 2 (Day 57 through Day 85)				Treatment Period 3[a] (Day 85 through Day 113)				
Event/Assessment	Day 1	Day 4 Telephone Call (±1 Day)	Day 15[b] Telephone Call (±1 Day)	Day 15[b] Visit (±3 Days)	Day 29 Visit (±3 Days)	Washout Day 29 to Day 56 (+3 Days)	Day 57 Visit	Day 60 Telephone Call (±1 Day)	Day 71[b] Telephone Call (±1 Day)	Day 71[b] Visit (±3 Days)	Day 85[c] Visit (±3 Days)	Day 86 Telephone Call	Day 87 Telephone Call	Day 99[b,d] Telephone Call (-11 Days)	Day 99[b,d] Visit (-11 Days)	Day 113 Visit (±3 Days)
Urine pregnancy test	X				X		X				X					X
Urine tests[q]	X			X	X		X			X	X				X	X
[redacted]																
Serum chemistry	X			X	X		X			X	X				X	X
Plasma chemistry[t]	X			X	X		X			X	X				X	X
Hematology	X				X		X				X					X
Inhaled study drug dose in clinic	X						X				X					
Meal or snack in clinic											X					
Ivacaftor dose in clinic[u]											X					
Dispense inhaled study drug	X						X				X					
Dispense ivacaftor											X					

[q] Urinalysis at Day 1, Day 29, Day 57, Day 85, and Day 113. Urine sodium, potassium, and creatinine analysis at Day 1, Day 15 (if a visit is planned), Day 29, Day 57, Day 71 (if a visit is planned), Day 85, Day 99 (if a visit is planned), and Day 113.

[redacted]

[u] Ivacaftor should be administered every 12 hours (q12h) with fat-containing food. The first dose of ivacaftor in Part B will be administered on the Day 85 Visit, after completion of the Day 85 pre-dose assessments.

Table 3-2 Study PS-G202: Treatment Period

	Part A						Part B									
	Treatment Period 1 (Day 1 through Day 29)						Treatment Period 2 (Day 57 through Day 85)					Treatment Period 3[a] (Day 85 through Day 113)				
Event/Assessment	Day 1	Day 4 Telephone Call (±1 Day)	Day 15[b] Telephone Call (±1 Day)	Day 15[b] Visit (±3 Days)	Day 29 Visit (±3 Days)	Washout Day 29 to Day 56 (+3 Days)	Day 57 Visit	Day 60 Telephone Call (±1 Day)	Day 71[b] Telephone Call (±1 Day)	Day 71[b] Visit (±3 Days)	Day 85[c] Visit (±3 Days)	Day 86 Telephone Call	Day 87 Telephone Call	Day 99[b,d] Telephone Call (-11 Days)	Day 99[b,d] Visit (-11 Days)	Day 113 Visit (±3 Days)
Instruct subject on Part B dietary and medication restrictions									X	X						
Dispense nebulizer base	X															
Dispense 2 handsets (aerosol heads) for nebulizer	X						X				X					
Instruct subject on proper use of nebulizer[v]	X		X	X			X		X	X	X			X	X	
[redacted]																
Collect unused study drug and perform study drug count					X						X					X
Collect subject diary					X						X					X
[redacted]																
Adverse events and serious adverse events	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X

[v] If inhaled study drug is administered in clinic, site staff should clean nebulizer before releasing to subject.

[redacted]

Table 3-3 Early Termination of Treatment Visit and Safety Follow-Up Telephone Call

Event/Assessment	Early Termination of Treatment Visit	Safety Follow-up Telephone Call 28 Days (± 7 Days) After Last Dose of Study Drug[a]
Clinic visit	X	
QOL-PCD[b]	X	
SGRQ[b]	X	
Height and weight[c]	X	
Pulse oximetry and vital signs [d]	X	
Full physical examination[e]	X	
12-lead ECG[f]	X	
[redacted]	[redacted]	
Spirometry	X	
Urine pregnancy test	X	
Hematology	X	
Urine tests[h]	X	
Serum chemistry	X	
Plasma chemistry[i]	X	
[redacted]	[redacted]	
[redacted]	[redacted]	
Collect unused study drug and perform study drug count	X	
Collect subject diary	X	
[redacted]	[redacted]	
Medication review	X	X
Concomitant treatments and procedures	X	X
Adverse events and serious adverse events	X	X

[a] If the subject prematurely discontinues study drug, an Early Termination of Treatment Visit should be scheduled as soon as possible after the subject decides to terminate study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Telephone Call, approximately 28 days (± 7 days) after their last dose of study drug.

[b] The QOL-PCD assessment must be completed before the start of any other assessments scheduled at this visit. The SGRQ should be completed immediately following the QOL-PCD.

[c] Height and weight will be measured with shoes off. BMI will be calculated.

[d] Vital signs and pulse oximetry will be performed after the subject has been seated or supine for at least 5 minutes.

[e] Physical examination of all body systems, excluding rectal and genitourinary examinations.

[f] The ECG will be performed after the subject has been seated or supine for at least 5 minutes. Prior to placing ECG leads, the record will be reviewed for the presence of dextrocardia. Subjects with dextrocardia will have all ECG limb and chest (V) leads reversed.

[redacted]

[h] Urinalysis and urine sodium, potassium, and creatinine analysis.

[i] Plasma potassium.

4 TABLE OF CONTENTS

List of Tables

List of Figures

Glossary of Terms

Abbreviation	Term
ACE	angiotensin converting enzyme
ADE	adverse device effect
AE	adverse event
ALT	alanine aminotransferase
ARB	angiotensin receptor blocker
ASL	airway surface liquid
AST	aspartate aminotransferase
ATP	adenosine triphosphate
ATS	American Thoracic Society
β-HCG	beta-human chorionic gonadotropin
bid	twice per day
BMI	body mass index
Ca^{++}	calcium
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane receptor protein
CFTR	CF transmembrane conductance regulator gene
CI	confidence interval
Cl^-	chloride ion
CPAP	continuous positive airway pressure
CRO	contract research organization
CS	compound symmetry
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
[redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ENaC	epithelial sodium channel
ERS	European Respiratory Society
ETT	Early Termination of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
$FEF_{25\%-75\%}$	forced midexpiratory flow, midexpiratory phase
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
G551D	CFTR missense gene mutation that results in the replacement of a glycine residue at position 551 of CFTR with an aspartic acid residue
GCP	Good Clinical Practice
GLI	Global Lung Function Initiative
GPS	Global Patient Safety
HEENT	head, eyes, ears, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HS	hypertonic saline
ICF	informed consent form

Abbreviation	Term
ICH	International Council on Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	Investigational New Drug (application) (US)
IRB	institutional review board
ISO	isoflurane-treated
IXRS	interactive response system in which X represents voice or web
K^+	potassium
LFT	liver function test
LMA	low melting-point agarose
max	maximum
MCC	mucociliary clearance
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency (United Kingdom)
min	minimum
N	total sample size
Na^+	sodium
NEP	neural endopeptidase
nNO	nasal nitric oxide
NPD	nasal potential difference
P	probability
pp	percent predicted
PBS	phosphate buffered saline
PCD	primary ciliary dyskinesia
PCL	periciliary layer
PK	pharmacokinetic(s)
PR	PR interval, segment
q12h	every 12 hours
QOL	quality of life
QOL-PCD	PCD Quality of Life Questionnaire
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
R117H	CFTR missense gene mutation that results in the replacement of an arginine residue at position 117 of CFTR with a histidine residue
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SGRQ	St. George's Respiratory Questionnaire
SUSAR	suspected, unexpected, serious adverse reaction
TE	treatment-emergent
TEM	transmission electron micrograph
TEAE	treatment-emergent adverse event
UADE	unanticipated adverse device effects

Abbreviation	Term
ULN	upper limit of normal
USA	United States of America
WHO-DDE	World Health Organization-Drug Dictionary Enhanced

5 INTRODUCTION

5.1 Background

Primary ciliary dyskinesia (PCD) is an autosomal recessive disorder characterized by various ciliary defects that result in loss of synchronous ciliary beating and ciliary propulsive function. In the ciliated airways of the lung, PCD is manifested by ineffective clearance of mucous secretions and inhaled particles, including bacteria. Clinical features of PCD include early onset of recurrent or persistent rhinitis, sinusitis, otitis media, bronchiectasis and bronchial infections.[1] About 50% of PCD patients have situs inversus or other laterality defects. Infertility occurs in nearly 100% of males due to immotile spermatozoa and females are often infertile due to impaired ciliary function in the fallopian tubes.[2] In addition to the clinical presentation, PCD patients have very low nasal nitric oxide (nNO) concentrations, ranging from 1/10th to 1/50th that of healthy subjects.[3,4] In addition, most patients have diagnostic ciliary defects on electron microscopic evaluations of ciliated airway cells.[1,5]

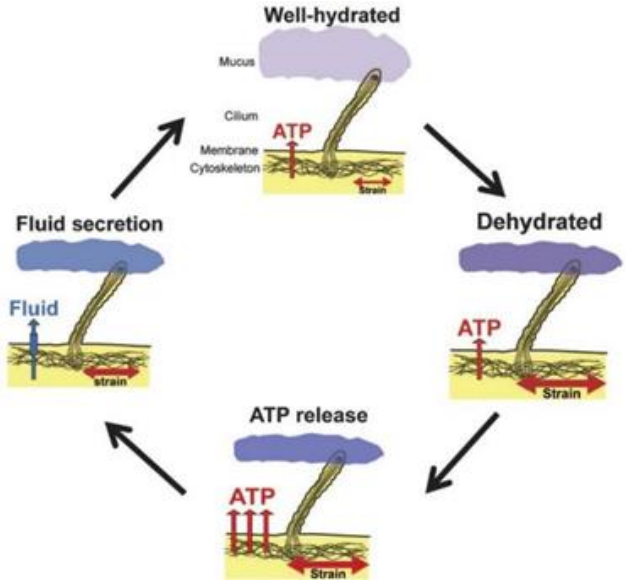
PCD has been reported in many ethnic groups without apparent racial or gender preference and, consistent with being an autosomal recessive disorder, it has been observed with a higher incidence in consanguineous and isolated populations.[6,7,8,9] The estimated incidence of PCD is 1 in 16,000 to 1 in 20,000 births.[10] To date, over 30 disease-causing genetic mutations have been identified that are associated with proteins that are critical for ciliary structure and function in PCD patients. The extent of ciliary dysfunction varies with the genetic defect in a particular patient, thus resulting in mutation-dependent rates and extent of loss of lung function.[11]

Currently, there are no approved treatments for PCD and no completed, industry-sponsored, controlled clinical studies to evaluate treatments for PCD.[12] Given the lack of demonstrated value of treatments, management of PCD patients is typically focused on clearance of airways along with prevention and treatment of airway infections. These therapies may include chest percussion, postural drainage, drugs to treat pulmonary symptoms and antibiotics (often oral). Given the importance of cough clearance in patients with PCD, the use of cough suppressants is avoided.

It has been classically believed that mucus clearance is affected by cilia (i.e., mucociliary clearance; MCC) and cough (i.e., cough dependent clearance). Because of the absence of cilial activity in PCD, it has been concluded that PCD reflects a simple loss of mechanical transduction of cilial force into mucus transport. This scenario is consistent with the gravitational distribution of PCD bronchiectasis, i.e., it is more prevalent in lower lobes.

However, it has been demonstrated that mucus clearance is more complicated than simply a combination of MCC and cough clearance and that mucus concentration is a major determinant of mucus transport. As a component of studies designed to explore how normal airways maintain mucus hydration (2% solids, 98% water) optimal for mucus transport, it was discovered that motile cilia sense the hydration status of mucus (see Figure 5-1).[13]

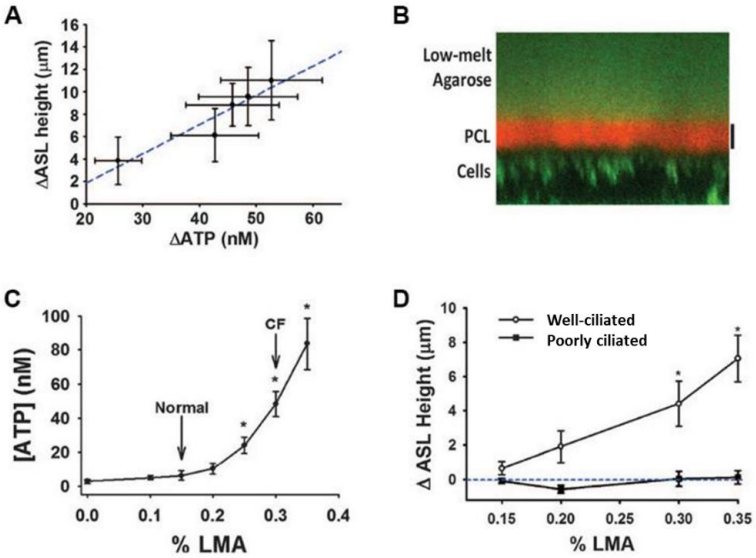
Figure 5-1 Proposed Feedback Model for PCL Hydration



Proposed feedback model of stimulation of adenosine triphosphate (ATP) release and subsequent fluid secretion by increased membrane stress during conditions of increased mucus concentration. Increased mucus concentration is sensed by beating cilia and leads to increased fluid secretion through ATP release. Once the mucus is rehydrated and has a lower viscoelasticity, the stress on the cilia is reduced, ATP release is decreased, and fluid homeostasis returns to the normal state (from Button 2013)[13].

The mechanism for the normal autoregulation of mucus hydration requires two elements: 1) strain on the cilial shaft, which is dependent on the interaction of a beating cilium and the concentration of mucus (i.e., a more concentrated mucus is more difficult to move) and which puts more strain on the cilial shaft/base; and 2) cilial strain-dependent release of ATP into the airway lumen, whereby ATP via interactions with purinoceptors inhibits epithelial sodium channel (ENaC)-dependent sodium (Na^+) (and fluid) absorption and accelerates cystic fibrosis transmembrane receptor (CFTR)- and calcium (Ca^{++})-activated chloride (Cl^-) channel-dependent fluid secretion. Thus, in PCD, the abnormally high rate of Na^+ absorption and low rate of Cl^- secretion that produces mucus hyperconcentration reflect the absence of normal regulation by extracellular ATP of ENaC and CFTR channels. Representative data showing the dependence of airway surface liquid (ASL) hydration on ATP concentrations and the dependence of ATP concentrations on motile cilia are shown in Figure 5-2.

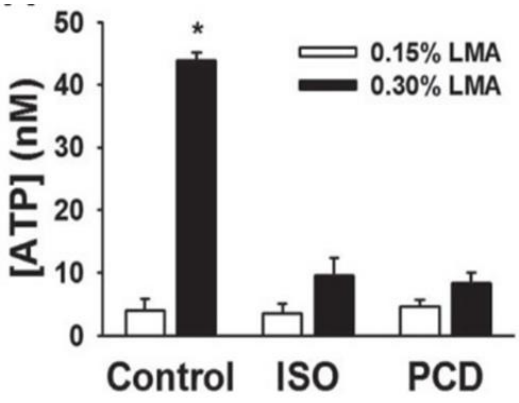
Figure 5-2 Dependence of ASL Hydration on ATP Concentration



(**A**) Relationship between the magnitude of changes in luminal ATP concentrations and ASL height. Human airway cultures were subjected to varying degrees of oscillatory stress before measuring luminal [ATP] and steady-state ASL height. These data revealed a direct relationship between ATP and changes in ASL height. (**B**) Sample ZX confocal micrograph showing the distinct layering of fluorescently labeled low melting-point agarose (LMA; green layer at top) from the periciliary layer (PCL) (labeled with Texas Red dextran). Airway epithelial cells were labeled green using calcein AM. Scale bar, 7 μm. (**C**) Relationship between the concentration of luminal ATP and the concentration of LMA added to the airway surface. Means ± SE from 6 to 8 cultures per point. **P* <0.05 compared to vehicle (0% LMA). (**D**) Relationship between the change in ASL height and concentration of LMA for both poorly ciliated and well-ciliated cultures. Data are plotted as the difference in ASL height between the LMA relative and a vehicle control (PBS) at 30 min after exposure. Without LMA, (PBS control), the average ASL height at 30 min was 8.2 ± 0.3 μm for the well-ciliated and 6.1 ± 0.4 μm for the poorly ciliated group. Mean ± SE from 3 cultures per point. **P* <0.05 compared to the initial measurement (from Button 2013).

As part of these studies, the question was asked whether the autoregulation of mucus/ASL hydration depended on motile cilia. Indeed, both an agent that acutely paralyzed cilial activity (isoflurane) and ciliated cultures from subjects with PCD revealed that motile cilia were required for this sensing mechanism (Figure 5-3). This observation led to the hypothesis that there may be a "second hit" in PCD mucus clearance, i.e., mucus hyperconcentration. Review of the literature revealed that PCD mucus was hyperconcentrated (dehydrated) to a degree similar to cystic fibrosis (CF).[14] [redacted]

Figure 5-3 PCD Cilia Model



Data summarizing the role of cilia beating in control, isoflurane-treated (ISO), and primary ciliary dyskinesia (PCD) airway cultures exposed to 0.15% LMA and 0.3% LMA. Data are means ± SE from three cultures per group. **P* <0.05 between groups (from Button 2013).

The poor clearance of PCD mucus as a function of increased concentration may not appear to be relevant to PCD subjects who have no cilial activity (i.e., no MCC). However, recent analyses suggest that mucus hyperconcentration is a major factor in the clearance of mucus by cough and all the elements of that process. For example, simple measures of cough clearance suggest that cough clearance is decreased as a function of the mucus concentration cubed.[16] Similarly, the disadhesion of mucus from the epithelial surface required for cough is heavily dependent on mucus concentration as is the "tearing" of mucus from adjacent mucus (i.e., mucus cohesion).[17,18] Thus it is predicted that normalization of mucus concentration in PCD subjects will greatly improve the efficiency of cough clearance.

Finally, there likely is a third mode of mucus clearance i.e., gas-liquid pumping. [19,20,21] Though described 30 years ago, little attention has been paid to this mode of transport. In essence, this transport reflects 3 variables: 1) there is hysteresis in shear on airway surfaces during normal respiration, so that shear is greatest on expiration; 2) entrainment of mucus flow by air; and 3) the friction generated by mucus flow over airway surfaces. Recent in vivo data support this mechanism in animals. Importantly, recent data have shown that the friction of mucus movement over airway surfaces is again highly dependent on mucus concentration, i.e., the higher the concentration, the higher the friction. Recent studies of mouse models of PCD suggest that gas-liquid pumping contributes to basal mucus flow in PCD animals. Therefore, it predicted that agents that normalize mucus concentration in PCD subjects, i.e., hydrating agents, will reduce mucus-airways surface friction and accelerate gas-liquid dependent mucus clearance.

In summary, it appears likely that the failure to clear mucus in PCD subjects reflects both the absence of cilial beat/force and the absence of normal regulation of mucus concentration. Mucus hyperconcentration is predicted to limit the effectiveness of the 2 "backup" mechanisms for mucus clearance in PCD subjects, i.e., cough and gas-liquid pumping. Consequently, restoring PCD mucus to its normal hydration status is predicted to be therapeutic in this population.

5.2 VX-371 Solution for Inhalation

VX-371 (Parion Sciences P-1037) 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. Sodium ions enter cells through apical ENaC and are transported out by the Na^+/ K^+ ATPase located at the basolateral membrane. 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. 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. It is hypothesized that the inhibition of ENaC activity with VX-371 will increase hydration of airway secretions rendering them more susceptible to cough clearance and gas-liquid pumping in subjects with PCD.

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

5.3 Ivacaftor

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

Kalydeco is indicated for the treatment of CF in patients as young as 2 years who have the *G551D* and certain other gating mutations as well the *R117H* mutation in the cystic fibrosis transmembrane conductance regulator gene *(CFTR)*. The indicated mutations and approved populations vary by country.

Additional information about ivacaftor is available in the Ivacaftor Investigator's Brochure.

5.4 Rationale for the Present Study

In PCD, the lack of ATP release into the lumen of the airways due to dysfunctional cilia leaves ENaC uninhibited, resulting in hyperconcentration of mucus. Inhibition of ENaC by VX-371 is expected to restore hydration of the mucus in PCD patients, resulting in improved cough clearance and gas-liquid pumping of mucus. [redacted]

The majority of PCD patients are expected to have intact CFTR function, although the regulation of CFTR activity by purinoceptors may be altered due to reduced airway luminal ATP. Ivacaftor improves chloride transport in vitro in normal human bronchial epithelial (HBE) cells that have intact CFTR, and in HBE cells from CF patients with various *CFTR* mutations, yielding increased ASL height.[22]

[redacted]

[redacted]

In Part A, the present study is designed to evaluate the safety and efficacy of VX-371 administered with and without 4.2% HS for 28 days to subjects with PCD who are ≥12 years of age. In Part B, the study is designed to evaluate the safety and efficacy of VX-371 administered with and without 4.2% HS in subjects treated with orally-administered ivacaftor.

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 ivacaftor.

6 STUDY OBJECTIVES

6.1 Part A Objectives

Primary

To evaluate the safety and efficacy of treatment with VX-371, administered with and without 4.2% HS, in subjects with PCD who are ≥12 years of age

Secondary

To evaluate the effect of VX-371, administered with and without 4.2% HS, on quality of life (QOL) in subjects with PCD who are ≥12 years of age

6.2 Part B Objectives

Primary

To evaluate the safety and efficacy of treatment with ivacaftor and VX-371, administered with and without 4.2% HS in subjects with PCD who are ≥12 years of age

Secondary

To evaluate the effect of ivacaftor and VX-371, administered with and without 4.2% HS on QOL in subjects with PCD who are ≥12 years of age

7 STUDY ENDPOINTS

7.1 Part A Endpoints

7.1.1 Primary Endpoints

- Results of safety and tolerability assessments of adverse events (AEs), clinical laboratory values (urine, serum and plasma chemistry, and hematology), 12-lead electrocardiograms (ECGs), spirometry, vital signs, and pulse oximetry
- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from study baseline, after 28 days of treatment in Part A

7.1.2 Secondary Endpoint

- Change in QOL score as measured by the Quality of Life-PCD Questionnaire (QOL-PCD) and the St. George's Respiratory Questionnaire (SGRQ) from study baseline, after 28 days of treatment in Part A

[redacted]

7.2 Part B Endpoints

7.2.1 Primary Endpoints

- Results of safety and tolerability assessments of AEs, clinical laboratory values (urine, serum and plasma chemistry, and hematology), 12-lead ECGs, spirometry, vital signs, and pulse oximetry
- Absolute change in $ppFEV_1$, from study baseline and Part B baseline after 28 days of treatment in Part B

7.2.2 Secondary Endpoint

- Change in QOL score as measured by the QOL-PCD and SGRQ from study baseline and Part B baseline, after 28 days of treatment in Part B

[redacted]

8 STUDY DESIGN

8.1 Overview of Study Design

This is a Phase 2a, 2-part, multicenter, randomized, double-blind, placebo-controlled, incomplete block crossover study in subjects ≥12 years of age with PCD.

Part A will consist of Treatment Period 1 and Treatment Period 2, separated by a Washout Period.

Part B is optional and will consist of Treatment Period 3; subjects will complete Part A before beginning Part B. There will not be a Washout Period between Part A and Part B.

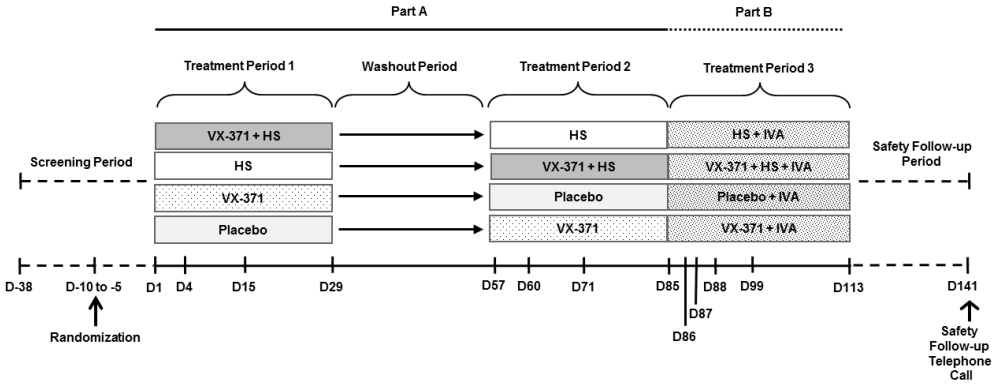
Approximately 150 subjects will be randomized to 1 of 4 treatment sequences in Part A. Subjects who enroll in Part B will have oral ivacaftor added to the treatment they were receiving in Treatment Period 2 of Part A, as described in Table 8-1.

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

Table 8-1 Study PS-G202 Treatment Sequences

	Part A		Part B	
Sequence	**Treatment Period 1**	**Treatment Period 2**	**Treatment Period 3**	**N**
1	VX-371 in 4.2% HS	4.2% HS	4.2% HS + ivacaftor	50
2	4.2% HS	VX-371 in 4.2% HS	VX-371 in 4.2% HS + ivacaftor	50
3	VX-371 in 0.17% saline	Placebo (0.17% saline)	Placebo (0.17% saline) + ivacaftor	25
4	Placebo (0.17% saline)	VX-371 in 0.17% saline	VX-371 in 0.17% saline + ivacaftor	25

Figure 8-1 Schematic of Study Design PS-G202



This study includes the following:

1. **Screening Period:** Day of Screening Visit until Day 1 (first dose of study drug). The Screening Visit can occur Day -38 to Day -5, relative to the first dose of study drug.
2. **Treatment Periods:**

   Part A:

   - Treatment Period 1: Day 1 (first dose of study drug) through Day 29 (28 days of treatment)
   - Washout Period: Day 29 through Day 56 (28 days)

- Treatment Period 2: Day 57 through Day 85 (28 days of treatment)

Part B (Optional):

- Treatment Period 3: Day 85 (first dose of oral ivacaftor) through Day 113 (28 days of treatment)

3. **Safety Follow-up Period**: 28 days (± 7 days) after the last dose of study drug.
4. **Early Termination of Treatment (ETT) Visit**: The ETT Visit is to occur as soon as possible after the subject decides to terminate study drug treatment.

8.1.1 Maintenance of Stable Medication Regimen for PCD

If the subject meets the criteria for study participation and is taking HS at the time of screening, the subject will be instructed to stop their usual regimen of inhaled HS for the duration of the study, beginning at least 28 days before the first dose of study drug in the study and continued through completion of the last study visit. If a subject is not taking HS as part of their ongoing PCD treatment, the Day 1 Visit may be scheduled to occur as soon as 5 days after the Screening Visit, provided that results of all screening procedures have been received. Each subject will be instructed to use an appropriate airway clearance technique throughout the study.

All concomitant medications and airway clearance measures/techniques should be kept on a stable regimen for the duration of the study, other than the discontinuation of use of HS during the Screening Period.

If taking daily chronic or chronic cycling antibiotics, the subject must have been on a consistent regimen for at least 4 months before the Screening Visit. The cycling regimen of antibiotics can be either intermittent monotherapy (e.g., 28 days on/28 days off) or continuous alternating therapy (e.g., 28-day cycles of 2 alternating antibiotics). For patients that take cycling antibiotics, with only 1 antibiotic, the first visit of Treatment Period 1 and Treatment Period 2 should be scheduled to occur on the same day of the subject's antibiotic cycle (e.g., if Day 1 falls on the 4th day of a cycle, Day 57 should fall on the 4th day of the same antibiotic cycle). For patients that take cycling, alternating antibiotics, the first day of Treatment Period 1 and Treatment Period 2 should be scheduled to occur on the same day of the subject's antibiotic cycle with the same drug (e.g., if Day 1 falls on the 4th day of a cycle with antibiotic #1, Day 57 should also fall on the 4th day of the cycle with antibiotic #1). Subjects who are on a stable chronic antibiotic regimen should remain on this regimen through completion of the last study visit.

8.1.2 Screening: Day -38 to Day -5

Screening Visit assessments are listed in Table 3-1.

The Screening Visit will occur between Day -38 and Day -5 before administration of the first dose of inhaled study drug to confirm that the subject meets the inclusion and exclusion 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. To prepare for study participation, subjects will be instructed on the study requirements for concomitant medications (Table 9-1 and Table 9-2).

At the Screening Visit, each subject will receive a test dose of 4.2% HS via a PARI eFlow nebulizer to confirm tolerability of inhaled HS. Pre-dose spirometry will be performed within 60 minutes before the test dose. Post-dose spirometry will be performed 60 (± 5) minutes after the test dose. If the subject's post-HS test dose spirometry value shows a 15-percentage point or

greater absolute reduction in $ppFEV_1$ compared to the subject's pre-HS test dose $ppFEV_1$ value, the investigator may either screen fail the subject or administer a short-acting bronchodilator to the subject.

If the subject is treated with a short-acting bronchodilator, spirometry will be repeated at least 10 minutes after administration of the short-acting bronchodilator. If the subject's post-short-acting bronchodilator $ppFEV_1$ value does not return to within 15 percentage points (absolute) of the subject's pre-HS test dose $ppFEV_1$ value, the investigator should screen fail the subject.

If the subject's $ppFEV_1$ returns to within 15 percentage points (absolute) of the pre-HS test dose value, the investigator may provide a short-acting bronchodilator for use before all doses of inhaled study drug are administered.

If the subject experiences a post-HS test dose absolute decline in $ppFEV_1$ less than 15 percentage points, the investigator may choose to provide a short-acting bronchodilator for use before all doses of inhaled study drug are administered.

While subjects can be screened based on evidence supportive of a PCD diagnosis, all subjects must meet the confirmatory diagnostic PCD criteria (including central review, as required) prior to randomization (Section 9.1).

Screen failures and reason for failure will be documented within the eCRF.

8.1.2.1 Repetition of Screening Assessment(s)

Repetition of individual screening assessment(s) that did not meet eligibility criteria is permitted 1 time for the following reasons:

- If there is clear evidence of a laboratory error (e.g., hemolyzed sample) or equipment malfunction.
- Exclusionary liver function test (LFT) levels and/or serum or plasma potassium levels.
- Collection of a repeat sample for a laboratory test or assessment, for any other reason, may be permitted only with prior approval of the Parion medical monitor.

If screening spirometry measurements fail to meet acceptability and repeatability criteria as specified by American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines, 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.

8.1.2.2 Rescreening

Subjects may be rescreened after investigator discussion with, and approval from, the Parion medical monitor. If a subject is rescreened, all Screening Visit assessments will be repeated except for PCD genotyping and follicle-stimulating hormone (FSH) level (if serum FSH level was ≥40 mIU/mL during prior screening). Subjects may only be rescreened once. If a subject is rescreened, the screening window will begin once the first rescreening assessment has been initiated.

8.1.2.3 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 8.1.2.1), and/or
- Unexpected operational or logistic delays, or to meet the eligibility criteria

8.1.3 Treatment Periods

Treatment Period assessments are listed in Table 3-2.

Subjects who prematurely discontinue study drug will complete an ETT Visit and will have a Safety Follow-up Telephone Call that is to occur 28 days (± 7 days) after the last dose of study drug, as described in Table 3-3, Section 8.1.4 and Section 8.1.5.

All reasonable efforts should be made to schedule clinic visits at the same time of day.

8.1.3.1 Part A

Part A comprises Treatment Period 1, the Washout Period, and Treatment Period 2.

8.1.3.1.1 Treatment Period 1

At the Day 1 Visit, the subject is required to continue to meet all inclusion and exclusion criteria (Sections 9.1 and 9.2) and continue to have stable PCD disease, in the opinion of the investigator. The first dose of inhaled study drug will be administered after randomization on Treatment Period 1 Day 1. Inhaled study drug should be taken according to instructions provided within the protocol. Study clinic visits will occur on Day 1 and Day 29 to allow for a full 28 days of treatment.

If the first dose of inhaled study drug administered in the clinic on Day 1 is taken in the morning, the second dose will be taken that evening. The last dose of the twice daily study regimen will be taken on the evening of Day 28 and no dose will be taken before the morning visit on Day 29.

If the first dose of inhaled study drug on Day 1 is taken in the clinic in the afternoon, a second dose will not be taken that evening. The last dose of the twice daily study regimen in Treatment Period 1 will be taken on the morning of Day 29, at least 4 hours before the Day 29 Visit.

Subjects should only take the inhaled study drug at a maximum of twice daily.

At Day 4 (± 1 day), subjects will have a telephone call from the study coordinator or authorized site designee for safety purposes to ascertain if there have been any AEs. If necessary to follow up on a new medical problem, the subject may be asked to return to clinic.

Subjects randomized prior to Independent Data Monitoring Committed (IDMC) approval to convert Day 15 Visit to a telephone call:

- If a subject reaches the Day 15 Visit prior to IDMC approval to convert the Day 15 Visit to a telephone call, the Day 15 Visit must be completed to assess safety parameters, including AEs, vital signs, pulse oximetry, ECG, physical exam, clinical laboratory values, and spirometry. No telephone call is required on this day if a visit is conducted.
- If the IDMC does not approve to convert the Day 15 Visit to a telephone call, subjects will proceed as per the bullet above.

Subjects randomized <u>after</u> IDMC approval to convert Day 15 Visit to a Telephone Call:

- The Day 15 Visit will be changed to a Day 15 Telephone Call to assess AEs. No visit is required on this day if a telephone call is conducted.

8.1.3.1.2 Washout Period

Subjects will undergo a Washout Period of 28 days (+ 3 days) between Treatment Period 1 and Treatment Period 2. Subjects should continue to maintain a consistent medication and airway clearance regimen throughout the Washout Period. The Washout Period may be extended for an additional 28 days for acute upper or lower respiratory infections following discussion and approval of the Parion medical monitor.

8.1.3.1.3 Treatment Period 2

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. If the subject does not meet these criteria, then the continuation of the subject into Treatment Period 2 should be discussed with the Parion medical monitor.

The first dose of inhaled study drug in Treatment Period 2 will be administered at the Day 57 Visit.

Study clinic visits will occur on Day 57 and Day 85 to allow for a full 28 days of treatment. If the dose of inhaled study drug administered in the clinic on Day 57 is taken in the <u>morning</u>, the second dose of inhaled study drug will be taken that evening. The last dose of the twice daily study regimen will be taken on the evening of Day 84 and no dose will be taken before the morning visit on Day 85.

If the first dose of inhaled study drug on Day 57 is taken in the clinic in the <u>afternoon</u>, a second dose of inhaled study drug will not be taken that evening. The last dose of the twice daily study regimen in Treatment Period 2 will be taken on the morning of Day 85, at least 4 hours before the Day 85 Visit.

Subjects should only take the inhaled study drug at a maximum of twice daily.

On Day 60, subjects will have a telephone call for safety purposes (e.g., inquire about adverse events). If necessary to follow up on a new medical problem, the subject may be asked to return to clinic.

Subjects randomized <u>prior to</u> IDMC approval to convert Day 71 Visit to telephone call:

- If a subject reaches the Day 71 Visit prior to the IDMC approval to convert the Day 71 Visit to a telephone call, the Day 71 Visit must be completed to assess safety parameters, including AEs, vital signs, pulse oximetry, ECG, physical exam, clinical laboratory values, and spirometry. No telephone call is required on this day if a visit is conducted.
- If the IDMC does not approve to convert the Day 71 Visit to a Telephone Call, subjects will proceed as per the bullet above.

Subjects randomized <u>after</u> IDMC approval to convert Day 71 Visit to telephone call:

- The Day 71 Visit will be changed to a Day 71 Telephone Call to assess AEs. No visit is required on this day if a telephone call is conducted.

8.1.3.2 Part B

Part B comprises Treatment Period 3 and is optional.

8.1.3.2.1 Treatment Period 3

In order to continue into Treatment Period 3 the subject must sign the Part B informed consent form (ICF) or assent, as applicable. The ICF should be signed before the Day 85 Visit to allow for delivery of study drug for Treatment Period 3.

Study visits will occur on Day 85 (also the last visit of Treatment Period 2) and Day 113 to allow for a full 28 days of study drug (inhaled study drug and oral ivacaftor).

On Day 86 and Day 87, until the telephone call is no longer required by the IDMC, subjects will have a telephone call for safety purposes (e.g., inquire about AEs). If necessary, the subject may be asked to return to clinic to follow up on a new medical problem.

The first dose of both ivacaftor and inhaled study drug in Treatment Period 3 will be administered at the Day 85 Visit, after completion of the Day 85 pre-dose assessments.

If the first dose of study drug (inhaled study drug and oral ivacaftor) administered in the clinic on Day 85 is taken in the morning, the second dose will be taken that evening. The last home dose of the twice daily study regimen in Treatment Period 3 will be taken on the evening of Day 112 and no dose will be taken on Day 113.

If the first dose of study drug (inhaled study drug and oral ivacaftor) administered in the clinic on Day 85 is taken in the afternoon, a second dose will not be taken that evening. The last home dose of the twice daily study regimen in Treatment Period 3 will be taken on the morning of Day 113, at least 4 hours before the Day 113 Visit.

Subjects should only take study drug at a maximum of twice daily.

Subjects will remain in the clinic for a total of 2 to 4 hours after dosing with study drug at the Day 85 Visit until the IDMC provides approval to only require subjects to remain in clinic for 1 hour post-dosing. The duration (2 to 4 hours) each subject stays in clinic for observation will be left to the discretion of the investigator. If the IDMC does not approve reducing the observation period to 1 hour post-dosing, then subjects will continue to be observed in clinic for 2 to 4 hours during the Day 85 Visit.

Subjects randomized prior to IDMC approval to convert Day 99 Visit to telephone call:

- If a subject reaches the Day 99 Visit prior to the IDMC approval to convert the Day 99 Visit to a telephone call, the Day 99 Visit must be completed to assess safety parameters, including AEs, vital signs, pulse oximetry, ECG, physical exam, clinical laboratory values, and spirometry. No telephone call is required on this day if a visit is conducted. The Day 99 Visit may occur at any time between Day 88 and Day 99.
- If the IDMC does not approve to convert the Day 99 Visit to a telephone call, subjects will proceed as per the bullet above.

Subjects randomized after IDMC approval to convert Day 99 Visit to telephone call:

- The Day 99 Visit will be changed to a Day 99 Telephone Call to assess AEs. No visit is required on this day if a telephone call is conducted. The Day 99 Telephone Call may occur at any time between Day 88 and Day 99.

8.1.3.3 Planned Pre-visit Subject Contacts

There are 5 planned **pre-visit** contacts to the subject during the study; 4 will occur in Part A and 1 will occur in Part B.

These contacts are to occur:

- Part A: 1 day before the Day 1, Day 29, Day 57, and Day 85 Visits
- Part B: 1 day before the Day 113 Visit

This planned pre-visit contact, which may occur via telephone call, text message, or email, is designed to ensure:

- that subjects remember to withhold their morning dose of study drug in Part A before the Day 29 and Day 85 Visit and in Part B before the Day 113 Visit only if the clinic visit is scheduled within 4 hours after the time of the morning dose,
- that subjects withhold their short-acting bronchodilator for 4 hours before spirometry is performed at the clinic in Part A at the Day 1, Day 29, Day 57, and Day 85 Visits, and in Part B before the Day 113 Visit,
- that subjects withhold long-acting bronchodilators the night before the first and last visit of each treatment period

[redacted]

- that subjects remember to bring their subject diary, all unused study drug, and [redacted] back to the clinic in Part A at the Day 29 and Day 85 Visits, and in Part B at the Day 113 Visit, and ETT Visit, if applicable.

All subjects will be asked to return their [redacted] at the Part A Day 29 and Day 85 Visits, the Part B Day 113 Visit, [redacted] at the Part A Day 85 Visit, the Part B Day 113 Visit, or their ETT Visit, as applicable.

Upon completion of the subject's last study visit and all study procedures, the pre-study medication regimen may be resumed at the discretion of the investigator.

8.1.4 Follow-Up

The Safety Follow-up Telephone Call is scheduled to occur 28 days (± 7 days) after the last dose of study drug for subjects who complete study drug dosing and for subjects who prematurely discontinue study drug dosing.

Based on a clinical finding during either Treatment Period or during the 28-day Safety Follow-up Period, the investigator may decide to convert the Safety Follow-up Telephone Call into a Safety Follow-up Visit, whereby the subject would be asked to return to the clinic.

8.1.5 Early Termination of Treatment

If the subject prematurely discontinues study drug treatment, an ETT Visit should be scheduled as soon as possible after the subject decides to terminate study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Telephone Call, approximately 28 days (± 7 days) after their last dose of study drug.

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

8.1.6 Unscheduled Visits

Subjects may need to be seen at times other than the scheduled study visits for additional safety assessments, to follow up on changes in clinical status, or to follow up on clinical laboratory or other findings. If an additional study visit occurs, the date and assessments completed during the visit will be documented.

8.1.7 Independent Data Monitoring Committee

An 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 study drug regimen to ensure the subjects' safety (Section 12.3.5). Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be included in the IDMC charter. The IDMC charter will be finalized before the first subject is screened.

8.2 Rationale for Study Design and Study Drug Regimens

8.2.1 Study Design

Part A of this Phase 2a, 2-part, randomized, double-blind, placebo-controlled, incomplete block, multicenter crossover study, in subjects with PCD ≥12 years of age is designed to evaluate the safety and efficacy of VX-371 formulated with or without HS. In Part B (optional), the safety and efficacy of ivacaftor and VX-371 formulated with or without HS will be evaluated. No controlled clinical study to evaluate the effect of a potential therapeutic agent has been completed at the time this protocol was written in subjects with PCD. Only recently have diagnostic criteria evolved that enable a confirmed diagnosis of PCD. Because many patients have been misdiagnosed in the past, this PCD study will restrict enrollment to only those subjects who meet the rigorous entry criteria.

A randomized, double-blind, placebo-controlled study design was selected for Part A to avoid observer bias and reduce symptoms or outcomes arising from the investigator's or the subject's knowledge of treatment. An incomplete block crossover design wherein subjects are randomized to 1 of 4 treatment sequences (Table 8-1) will enable within-subject comparison of the treatment effects with increased statistical power while maximizing the power for the comparisons anticipated to be of greatest interest. In Part B, administration of ivacaftor will be open-label, but subjects will remain blinded to the inhaled study drug treatment regimen and sequence.

During Part A, a 28-day Washout Period is judged to be of sufficient duration for all subjects to return to their baseline values for FEV_1. Multiple comparisons will be made which will provide insight with respect to the effect of VX-371 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 both 0.17% saline (placebo) and 4.2% HS since each subject will receive treatment with only 1 saline concentration; no subject will cross over from 0.17% saline to 4.2% HS or vice versa. The double blind will also be maintained with regard to VX-371 because allocation to this component will remain unknown to both investigators and subjects.

Given the absence of historical information from prior studies in PCD and the abundance of information in CF, another muco-obstructive disease, several extrapolations have been made

regarding the chosen endpoints from CF studies and applied to this PCD study. Change in $ppFEV_1$ was selected as the primary assessment of efficacy, based on observed effects of hydrating agents in CF, and based on observations that oral antibiotics can increase $ppFEV_1$ in treated PCD patients, which indicates that FEV_1 may be an acceptable measure. In addition, 2 quality of life instruments (i.e., questionnaires), the QOL-PCD and SGRQ, will be used. [redacted]

While chronic cycling antibiotics are not widely used in PCD patients, the scheduling of study drug with regard to the antibiotic schedule should be controlled while the subject is enrolled in the study as antibiotics may affect spirometry results in the PCD population (Section 8.1.1).

A sample size of approximately 150 subjects randomized is considered feasible and is expected to provide sufficient data to evaluate the safety and efficacy of VX-371 formulated with and without HS in Part A along with the administration of oral ivacaftor in Part B.

Part B was designed to evaluate whether the addition of oral ivacaftor will have an impact on the efficacy of inhaled VX-371. Therefore, no Washout Period between Treatment Period 2 and Treatment Period 3 is necessary.

8.2.2 Study Drug Dose and Duration

[redacted] Thus, Part A of the current study is designed to demonstrate safety and efficacy of an 85 µg dose of VX-371 administered twice daily, with or without HS, by oral inhalation in patients with PCD.

Parion Sciences Study PS-G201 was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of 85 µg VX-371 twice daily in subjects with CF. [redacted]

In Part B, subjects will continue on their inhaled study drug regimen from Treatment Period 2, and will also receive 150 mg of ivacaftor every 12 hours (q12h) for 28 days through Day 113 (see the Ivacaftor Investigator's Brochure for additional details supporting the efficacy, safety, and pharmacokinetic (PK) profile of ivacaftor).

8.2.3 Rationale for Study Assessments

Spirometry: Spirometry (as measured by FEV_1) is the most widely implemented standardized assessment to evaluate lung function.[24] 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, indicates that FEV_1 may be an equally acceptable measure in efficacy studies of the PCD population.

QOL-PCD: The QOL-PCD is a subject-completed, disease-specific instrument designed to measure impact on overall health, daily life, perceived well-being and symptoms that has been developed specifically for use in subjects with a diagnosis of PCD.[25,26]

SGRQ: The SGRQ is a 50-item questionnaire with 76 weighted responses. This questionnaire measures health status (quality of life) in patients with diseases of airway obstruction.[27] It has good discriminative and evaluative properties and is responsive to therapeutic trials.

The items in the SGRQ are divided into 3 domains: “Symptoms,” which is concerned with frequency and severity of respiratory symptoms; “Activity,” which is concerned with activities that cause or are limited by breathlessness; and “Impacts,” which covers aspects concerned with social functioning and psychological troubles resulting from airway disease. A score will be calculated for each domain and a total score will also be calculated. For each domain and for the total score, the range of values is 0 to 100, with higher values corresponding with greater impairment of quality of life. A minimum change in score of 4 units was established as clinically relevant after patient and clinician testing.

[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 instructions for use.
4. The subject must have evidence supportive of a PCD diagnosis, based on the following[redacted]:

[redacted]

5. Subjects with ppFEV$_1$ of ≥40 to <90 percentage points adjusted for age, sex, and height according to the Global Lung Function Initiative (GLI) predicted values at the Screening Visit, taken 4 hours or more after last dose of short-acting bronchodilators (β-agonists and/or anticholinergics)
6. Non-smoker for the past 90 days prior to the Screening Visit and less than a 5 pack-year lifetime history of smoking, and willing to not smoke while enrolled in the study.
7. Stable regimen of medications and chest physiotherapy for the 28 days prior to Day 1, and no anticipated need for changes during the study period (other than stopping inhaled HS).
8. If currently using daily inhaled HS, must be able to discontinue its use for the duration of the study.
9. If taking daily chronic or chronic cycling antibiotics, has been on a consistent regimen for at least 4 months prior to the Screening Visit. The cycling regimen of antibiotics can be either intermittent monotherapy (e.g., 28 days on/28 days off) or continuous alternating therapy (e.g., 28-day cycles of 2 alternating antibiotics).
10. Clinically stable (as deemed by the investigator) for at least 14 days prior to the Screening Visit with no evidence of significant new or acute respiratory exacerbations, excluding symptoms of allergic (perennial or seasonal) or non-allergic rhinitis.
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, Day 57, and Day 85 Visits before receiving the first dose of study drug in each Treatment Period, respectively. Subjects of childbearing potential and who are sexually active must meet the contraception requirements outlined in Section 11.6.5.1.

9.2 Exclusion Criteria

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

1. Diagnosis of CF, including at least 1 of the following:
   a. Documented sweat chloride test ≥60 mM by quantitative pilocarpine iontophoresis

   b. Abnormal nasal potential difference (NPD) test
   c. 2 CF-causing mutations in the CFTR gene
2. Subjects with only 1 mutation in the CFTR gene **and** a sweat chloride test ≥60 mM by quantitative pilocarpine iontophoresis.
3. History of any organ transplantation or lung resection or chest wall surgery.
4. Significant congenital heart defects, other than a laterality defect, at the discretion of the investigator.
5. Diagnosis of Cri du chat syndrome (chromosome 5p deletion syndrome).
6. Inability to withhold short-acting bronchodilator use for 4 hours prior to clinic visit and long-acting bronchodilator use the night before the first and last clinic visit of each treatment period.
7. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This may include, but is not limited to history of clinically significant and uncontrolled adrenal, neurologic, gastrointestinal, renal, hepatic, cardiovascular (including hyper/hypotension and tachy/bradycardia), psychological, pulmonary (other than PCD), metabolic, endocrine, or hematological/coagulation disorder or disease, or scoliosis of such severity that it impacts pulmonary function or any other major disorder or disease, in the opinion of the investigator.
8. Use of diuretics (including amiloride) or renin-angiotensin antihypertensive drugs (e.g., spironolactone, angiotensin converting enzyme [ACE] and/or neural endopeptidase [NEP]-inhibitors, or angiotensin receptor blockers [ARBs]) or trimethoprim or drospirenone in the 28 days before Day 1 or anticipate need for these medications during the study.
9. Had symptoms of acute upper or lower respiratory tract infection or had an acute pulmonary exacerbation requiring treatment or was treated with systemic antibiotics for ear or sinus disease within 28 days before Day 1 (topical otic antibiotics allowed).
10. History of significant intolerance to inhaled HS, as determined by the investigator.
11. History of drug or alcohol abuse, in the opinion of the investigator.
12. Known hypersensitivity to any of the study drugs or amiloride.
13. Used ivacaftor within 28 days prior to Day 1 or anticipate need for ivacaftor during the study.
14. Pregnant and/or nursing females.
15. Any clinically significant laboratory abnormalities at the Screening Visit as judged by the investigator, or any of the following:
   a. Plasma or serum potassium > upper limit of normal (ULN)
   b. Abnormal renal function, defined as creatinine clearance rate <50 mL/min using the Bedside Schwartz equation (for subjects 12 to 17 years of age)[29] or <50 mL/min using the Cockcroft-Gault equation (for subjects ≥18 years of age).[30]

c. Abnormal liver function, defined as ≥3 × ULN for alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or >2 × ULN for total bilirubin, unless accounted for by Gilbert's syndrome (benign indirect hyperbilirubinemia)
d. Hemoglobin concentration <10.0 g/dL

16. Unwilling or unable to follow the contraception guidelines as outlined in Section 11.6.5.1.
17. History of at least 2 sputum or throat swab cultures yielding *B. cepacia* complex or *M. abscessus* or *M. avium* within the previous 2 years.
18. Has had surgery within 3 months of Day 1 that required general anesthesia and hospitalization.
19. Has previously participated in an investigational study involving administration of any investigational compound or use of an investigational device within 28 days prior to the Screening Visit (Note: Participation in a past or concurrent observational study is acceptable).
20. Has any surgical or medical condition which in the judgment of the investigator might interfere with the absorption, distribution, metabolism, or excretion of the study drug or with safety evaluations.
21. Has any other condition or circumstances that, in the opinion of the investigator, should disqualify this subject for this study.
22. The subject or a close relative of the subject is the investigator or a sub-investigator, research assistant, pharmacist, study coordinator, or other staff directly involved in the conduct of the study.

9.2.1 Additional Exclusion Criteria for Part B

In addition to the exclusion criteria above, subjects who participate in Part B and meet any of the following exclusion criteria will **not** be eligible to continue into Part B.

1. Unable to swallow tablets.
2. Concomitant use of strong or moderate inhibitors or inducers of cytochrome P450 (CYP) 3A, including consumption of certain herbal medications (e.g., St. John's Wort), and grapefruit/grapefruit juice.
3. Known hypersensitivity to ivacaftor.

9.3 Study Restrictions

Prohibited and restricted medications are not allowed in this study (Screening Period through the last study visit) as summarized in Table 9-1 and Table 9-2.

Table 9-1 Prohibited Medications

		Part A			Part B	
Prohibited Medication	**Screening Period**	**Treatment Period 1**	**Washout Period**	**Treatment Period 2**	**Treatment Period 3**	**Until Safety Follow-Up Telephone Call**
• Hypertonic saline • Diuretics (including amiloride) • Renin-angiotensin antihypertensive drugs (ACE and/or NEP-inhibitors or ARBs) • Trimethoprim • Drospirenone	None allowed within 28 days before Day 1	None allowed	None allowed	None allowed	None allowed	Used as prescribed by subject's health care provider
Medications with moderate or potent CYP3A inhibitor activity, as well as grapefruit/ grapefruit juice	Used as prescribed by subject's health care provider	Used as prescribed by subject's health care provider	Used as prescribed by subject's health care provider	Used as prescribed by subject's health care provider	None allowed	Used as prescribed by subject's health care provider beginning 48 hours after the subject's last dose of ivacaftor
Moderate or potent CYP3A inducers including certain herbal medications such as St. John's Wort	Used as prescribed by subject's health care provider	Used as prescribed by subject's health care provider	Used as prescribed by subject's health care provider	Used as prescribed by subject's health care provider	None allowed	Used as prescribed by subject's health care provider beginning 48 hours after the subject's last dose of ivacaftor

Table 9-2 Antibiotic and Bronchodilator Restrictions

		Part A			Part B	
Restricted Medication	**Screening Period**	**Treatment Period 1**	**Washout Period**	**Treatment Period 2**	**Treatment Period 3**	**Until Safety Follow-up Telephone Call**
Chronic or chronic cycling antibiotics	Must have been on a consistent regimen for at least 4 months prior to the Screening Visit	Must remain on the pre-study regimen	Must remain on the pre-study regimen	Must remain on the pre-study regimen	Must remain on the pre-study regimen	Used as prescribed by subject's health care provider
Long-acting bronchodilators	Should be used at the same time of day, on the same schedule as during the 28 days before Day 1, unless medically necessary	Should be used at the same time of day, on the same schedule, every day Must be withheld the night before the clinic visit on Day 1 and Day 29, unless medically necessary.	Should be used at the same time of day, on the same schedule, every day Must be withheld the night before the clinic visit on Day 57, unless medically necessary.	Should be used at the same time of day, on the same schedule, every day Must be withheld the night before the clinic visit on Day 57 and Day 85, unless medically necessary.	Should be used at the same time of day, on the same schedule, every day Must be withheld the night before the clinic visit on Day 85 and Day 113, unless medically necessary.	Used as prescribed by subject's health care provider
Short-acting bronchodilators	Must be withheld for 4 hours prior to spirometry performed at the clinic visit, unless medically necessary	Must be withheld for 4 hours prior to spirometry performed at the clinic visit, unless medically necessary	Must be withheld for 4 hours prior to spirometry performed at the clinic visit, unless medically necessary	Must be withheld for 4 hours prior to spirometry performed at the clinic visit, unless medically necessary	Must be withheld for 4 hours prior to spirometry performed at the clinic visit, unless medically necessary	Used as prescribed by subject's health care provider

9.4 Prior and Concomitant Medications

Subjects are to remain on a stable PCD medication regimen from 28 days before Day 1 through the last study visit. Those patients taking HS before the Screening Period will washout from HS during the Screening Period and will not be allowed to take HS for the duration of the study

through the end of the last study visit (other than as blinded study drug if allocated to an HS-containing treatment sequence).

The following guidelines for bronchodilator use should be adhered to:

- Throughout the study, short- and long-acting bronchodilators should be used on the same time of day and schedule as during the 28 days before Day 1.
- Short-acting bronchodilators must be withheld for 4 hours prior to spirometry performed at the clinic visit and long-acting bronchodilators must be withheld the night before each clinic visit. Short- and long-acting bronchodilators may be taken by the subject if medically necessary.

Information regarding all prior and concomitant medications, including the subject's PCD medications, other medications, and herbal and naturopathic remedies administered from 28 days before the Screening Visit through the Safety Follow-up Telephone Call 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.

9.4.1 Prohibited Medications in Part B

Prohibited and restricted medications are described in Table 9-1 and Table 9-2.

Subjects who participate in Part B must not use medications with moderate or potent cytochrome P450 (CYP)3A inhibitor or inducer activity, and should not use certain herbal medications, grapefruit, or grapefruit juice beginning on Day 85 until 48 hours after the last dose of ivacaftor.

Subjects must not use commercially-available ivacaftor during the study.

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

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 Parion Sciences for safety, behavior, noncompliance with study procedures, or administrative reasons. If a subject has been withdrawn from study drug treatment, the subject will continue to be followed, provided the subject has not withdrawn consent.

Subjects who discontinue study drug early should continue to return for study assessments, as noted in Section 8.1.5.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for an ETT Visit, if applicable (see Section 8.1.5), and follow up with the subject regarding any unresolved AEs. The site staff should perform the Safety Follow-up Telephone Call with the subject 28 days (± 7 days) after the last dose of study drug.

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

A subject will be withdrawn from study drug for any of the following reasons:

- Parion Sciences, 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.
- A subject's treatment is unblinded by the investigator.
- Development of a life-threatening AE or a serious adverse event (SAE) that places him/her at immediate risk, and discontinuation of study drug deemed necessary.

A subject may be withdrawn from study drug after a discussion between the investigator and the Parion 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.
- A serum potassium level >1.1 × ULN, confirmed by a plasma potassium level >1.1 × ULN. A confirmatory serum and plasma 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 11.6.2.1 for further guidance on treatment of hyperkalemia.
- The subject has a relative decline in ppFEV$_1$ of ≥15% from their Day 1, Day 57, or Day 85 Visit pre-dose value.
- An increase in ALT or AST according to evaluations and management described in Section 11.6.2.2.

9.6 Replacement of Subjects

Subjects who withdraw or are withdrawn during the study drug treatment period(s) or washout period 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 Inhaled Study Drug Administration Via the Nebulizer

Inhaled study drug will be administered twice daily by a PARI eFlow nebulizer. The nebulizer will be provided to the subject for use with the inhaled study drug, and has been customized to be used *only* with the inhaled study drug provided for this study and is not to be used for the

inhalation of other treatments. Additionally, it is important that the subject use the provided nebulizer for the inhalation of study drug and not use any other PARI eFlow nebulizer 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 (nebulizer and handset/aerosol head) identification information will be documented for each subject.

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

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

10.2.2 Ivacaftor

For subjects enrolled in Part B of the study, the first dose of oral ivacaftor will be administered at the Day 85 Visit. A fat-containing meal or snack will be provided for ivacaftor dosing at the clinic. Subjects are required to take 150 mg of ivacaftor orally q12h with fat-containing food, such as a high-fat, high-calorie meal or snack. Examples of appropriate fat-containing foods will be provided in the Study Reference Manual.

10.2.3 Dosing in Clinic

This study requires that the first dose of study drug during each Treatment Period be taken in the clinic (at the Day 1, Day 57, and Day 85 Visits) while the subject is under observation by the study staff for at least 1 hour after dosing.

The post-dose observation period is generally anticipated to encompass the first hour after dosing at Day 1 and Day 57, at which time spirometry, chest auscultation, pulse oximetry, and vital signs will be repeated. If the subject is doing well and is in no respiratory distress, the subject will be allowed to leave the clinic after this period and will be given 28 days of the study drug for at-home administration. If, however, in the judgment of the investigator, the subject needs to continue to be observed or monitored, the length of the post-dose observation period may be extended.

Until the IDMC allows a 1-hour post-dose observation period at Day 85, subjects who continue into Part B will remain in clinic during the Day 85 Visit for 2 to 4 hours after administration of study drug. The amount of time each subject remains in clinic for observation (2 to 4 hours) may be left up to the discretion of the investigator. Prior to discharge, spirometry, chest auscultation, pulse oximetry, and vital signs will be repeated. If the subject is doing well and is in no respiratory distress, the subject will be allowed to leave the clinic after this period and will be given 28 days of the study drug for at-home administration. If, however, in the judgment of the investigator, the subject needs to continue to be observed or monitored, the length of the post-dose observation period may be extended.

If the subject routinely uses a short-acting bronchodilator prior to any inhalation treatment(s) (i.e., pre-treat), this practice should be continued throughout the study prior to inhalation of the inhaled study drug. If the subject does not routinely pre-treat inhaled medications with a short-

acting bronchodilator, but has demonstrated significant respiratory symptoms after the test-dose of HS at the Screening Visit, as determined by the investigator or an absolute decline in $ppFEV_1$ of ≥15 percentage points following the first dose of blinded inhaled study drug at Day 1, then the subject should be provided with a short-acting bronchodilator, as needed, and instructed to subsequently pre-treat with this medication prior to all subsequent doses of blinded inhaled study drug.

10.2.4 Dosing at Home

If the first dose of study drug administered in the clinic on Day 1, Day 57, or Day 85 is taken in the morning, the second dose will be taken that evening. The last dose of the twice daily study regimen will be taken on the evening of Day 28, Day 84, or Day 112 and no dose will be taken before the morning visit on Day 29, Day 85, or Day 113.

If the first dose on Day 1, Day 57, or Day 85 is taken in the clinic in the afternoon, a second dose will not be taken that evening. The last dose of the twice daily study regimen will be taken on the morning of Day 29, Day 85 or Day 113, at least 4 hours before the afternoon visit on Day 29, Day 85, or Day 113.

Subjects will be instructed to administer the study drug (inhaled study drug and/or oral ivacaftor) twice daily approximately 12 hours apart. Whenever possible, subjects should take the study drug at the same time each day. For example, the morning dose could be taken at 8:00 AM every morning and the evening dose could be taken at 8:00 PM every evening.

All inhaled study drug will be administered twice daily via the PARI eFlow nebulizer over an estimated 6 to 8 minutes.

Subjects will be asked to record the time start and stop of study drug dosing in a subject diary provided to them at Day 1, Day 57, and Day 85.

10.2.5 Missed Doses

On Non-Clinic Visit Days:

- If a subject misses a dose of study drug (inhaled study drug and/or oral ivacaftor) and remembers the missed dose within 6 hours, the subject should take the dose of study drug (with a fat-containing food, if oral ivacaftor).
- If more than 6 hours have elapsed after the usual dosing time, the subject should skip that dose of 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 Clinic Visit Days:

- If a subject misses a dose of study drug (inhaled study drug and/or oral ivacaftor) on a Study Visit day, the subject should take the dose (with a fat-containing food, if ivacaftor), unless it is within 4 hours of a clinic visit, and should alert site personnel upon arrival to the site.

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 in Part A to one of the 4 treatment sequences, (Treatment Sequence 1 or Treatment Sequence 2; Treatment Sequence 3 or Treatment Sequence 4), 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 is administered in Part A on Day 1.

An interactive web or voice response system (IXRS) will be used to assign subjects to treatment. The randomization code will be produced by a qualified randomization vendor. The Parion Sciences study biostatistician, or designee, will review and approve the dummy randomization list. The final randomization list will be reviewed and approved by a designated unblinded biostatistician.

There is no randomization in Part B. Subjects will remain in the same treatment as in Treatment Period 2 of Part A and will also receive open-label oral ivacaftor. Subjects must be able to meet and comply with study drug restrictions for Part B as outlined in Table 9-1 and Table 9-2 and per the Study Reference Manual.

10.4 Dose Modification for Toxicity

Modifications of the study drug doses are prohibited. If any unacceptable toxicity arises, individual subjects will be withdrawn from the study and study drug dosing will be discontinued. Interruptions of study drug dosing may be considered on a case-by-case basis after discussion with the Parion medical monitor.

Specific instructions for interruption for elevated liver function tests (LFTs) and elevated plasma and serum potassium are provided in Section 11.6.2.

10.5 Packaging and Labeling

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

Ivacaftor 150-mg tablets will be supplied in weekly, child resistant, 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 oral ivacaftor will be included in the Pharmacy Manual.

10.6 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, nebulizers, and handsets (aerosol heads) will be accounted for via the drug accountability forms as instructed by Parion Sciences.

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)

Table 10-1 Study Drug

Drug Name	Formulation/ Route	Dosage	Packaging	Storage Condition
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 in 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)
Ivacaftor	Blue, film-coated tablet with wax/oral	150 mg	Supplied as 150-mg tablets	Store at ≤ 25°C (77°F) with excursions to 30°C (86°F)

10.7 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 the subjects; (3) nebulizer and/or handset (aerosol head) dispensed [redacted] by the subjects; and (4) study drug returned by the subjects. [redacted] These materials will be retained at the site according to instructions provided by Parion Sciences or its designee until inventoried by the study monitor. The study monitor will review study drug records and inventory throughout the study.

10.8 Disposal, Return, or Retention of Unused Drug

The 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 Parion Sciences. Destruction will be adequately documented. Procedures for destruction or return of the study drug will be detailed in the Pharmacy Manual.

10.9 Compliance

To maximize treatment compliance, the investigator or designee will supervise all study drug dosing that occurs at the site. At each visit, site personnel will review that the subject is compliant with study drug dosing and remind the subject of study drug dosing requirements.

Compliance will also be assessed by ongoing count of study drug and evaluation of the subject diary.

Discrepancies will be discussed with the subject. If subjects demonstrate continued noncompliance of study drug dosing despite educational efforts, the investigator will contact the Parion medical monitor to discuss discontinuing the subject from the study drug.

10.10 Blinding and Unblinding

This is a double-blind study for the inhaled study drug and treatment assignment for Parts A and B. Treatment with ivacaftor in Part B will be unblinded (i.e., open-label).

10.10.1 Blinding

All study personnel will be blinded to subject treatment assignments 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 their 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
- Contract research organization (CRO) IXRS management
- Clinical Supply Chain Vendor
- IDMC
- Vendor preparing the unblinded analysis for the IDMC
- The bioanalytical laboratory/vendor personnel
- Parion medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time.

10.10.2 Unblinding

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

Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study drug 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 Parion medical monitor to discuss and agree to the need for unblinding. If investigators deem it not necessary to unblind immediately, they should first attempt to contact the Parion medical monitor to discuss and agree to the need for unblinding. If investigators have tried but are unable to reach the Parion 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 Parion medical monitor.

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

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the Parion 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 Parion Sciences, Vertex Pharmaceuticals, 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 and Parion Sciences or designee, per Section 13.1.2.2.

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

11 ASSESSMENTS

11.1 Timing of Assessments

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

The QOL-PCD assessment must be completed before the start of any other assessments. The SGRQ should be completed immediately following the QOL-PCD.

[redacted]

Subjects who have taken their morning dose of study drug may have a study visit and undergo visit assessments on that day, provided that the pre-dose assessments do not occur within 4 hours of the morning dose of study drug.

[redacted]

11.2 Subject and Disease Characteristics

Medical history will be elicited from each subject at the Screening Visit. 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.

Subject and disease characteristics include the following: demographics, medical history, height, weight, nNO level, type of laterality defect (situs inversus totalis, situs ambiguous, or heterotaxy) confirmed by historical chest imaging (if applicable), and PCD genetic mutation (determined by central genetic testing laboratory). PCD diagnostic criteria listed in Section 9.1 will be reviewed centrally, as defined in the Study Reference Manual.

[redacted]

[redacted]

11.5 Efficacy

11.5.1 Spirometry

Spirometry will be performed according to the ATS Guidelines (ATS, 2005) at the time points outlined in Table 3-1, Table 3-2, and Table 3-3. ATS criteria for acceptability will be determined via a central spirometry vendor. 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.

The first spirometry assessment at each visit should occur at least 4 hours after use of any short-acting β-adrenergic (e.g., albuterol) or anticholinergic (e.g., ipratropium) bronchodilator, and after a long-acting bronchodilator has been held from the previous evening, if applicable (see Section 9.4)

The following parameters will be determined as part of the spirometry assessment (according to GLI-predicted values for age, sex, and height).[31]

- Measured:
  - FEV_1 (L)
  - Forced vital capacity (FVC) (L)
  - Forced midexpiratory flow rate ($FEF_{25\%-75\%}$) (L/sec)
- Derived from measured parameters:
  - $ppFEV_1$ (percentage points)
  - ppFVC (L)
  - FEV_1/FVC and $ppFEV_1$/FVC
  - $ppFEF_{25\%-75\%}$ (L/sec)

For each assessment time point, a minimum of 3 acceptable maneuvers should be done. The largest FVC and second largest FVC must not vary by more than 0.15 L and the largest FEV_1 and the second largest FEV_1 must not vary by more than 0.15 L. Reproducibility criteria may require that up to 8 maneuvers be performed. Volume-time or flow-volume curves from the best

3 FVC maneuvers should be considered when entering the relevant spirometry data into the spirometry system.

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

Records of all spirometry maneuvers must be retained in the subject's source records.

11.5.2 QOL-PCD

The QOL-PCD will be completed before the start of any other assessments, including the SGRQ, as noted in Table 3-2 and Table 3-3.

Subjects aged 12 at Day 1 will complete the QOL-PCD-Child version themselves and their parents/caregivers will complete the QOL-PCD-Parent version on all visits, regardless of whether subjects subsequently become 13 years of age during the study. Subjects aged 13 to 17 years at Day 1 will complete the Adolescent version of the questionnaire themselves at all visits. Subjects aged 18 years and older at Day 1 will complete the Adult version of the questionnaire themselves at all visits. The questionnaires provide information about demographics; general quality of life, school, work, or daily activities; and symptom difficulties (pertaining to PCD). Copies of the QOL-PCD used in this study will be provided in the Study Reference Manual. Translations of the QOL-PCD, if available, will be provided for participating centers in non-English-speaking countries.

11.5.3 SGRQ

The SGRQ will be completed immediately following the QOL-PCD and before the start of any other assessments, as noted in Table 3-2 and Table 3-3.

Subjects aged 16 years or older at Day 1 will complete the SGRQ for themselves. [redacted]. Copies of the SGRQ used in this study will be provided in the Study Reference Manual. Translations of the SGRQ, if available, will be provided for participating centers in non-English-speaking countries.

11.6 Safety

Safety evaluations will include AEs, airway reactivity (pre- to post-dose FEV_1 change for first dose), clinical laboratory values, clinical evaluation of vital signs, ECGs, physical examinations, and pulse oximetry.

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. At the Screening Visit, blood specimens will be collected for safety laboratory tests. On Day 1, Day 57, and Day 85, blood samples will be collected before the first dose of the study drug in the corresponding Treatment Period.

Blood and urine samples for clinical laboratory assessments will be collected as shown in Table 3-1, Table 3-2, and Table 3-3. Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

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

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urine Tests[a]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen	Hematocrit	Nitrite
Creatinine	Erythrocytes:	Urobilinogen
Potassium	Mean corpuscular hemoglobin	Urine protein
Sodium	Mean corpuscular hemoglobin concentration	pH
Calcium		Urine blood
Chloride	Mean corpuscular volume	Specific gravity
Magnesium	Platelets	Urine ketones
Bicarbonate	Reticulocytes (absolute)	Urine bilirubin
Phosphorus	Leukocytes	Urine creatinine
Bilirubin, direct bilirubin	Differential (absolute and percent):	Urine glucose
Alkaline phosphatase	Eosinophils	Urine potassium
Aspartate aminotransferase	Basophils	Urine sodium
Alanine aminotransferase	Neutrophils	
Amylase	Lymphocytes	
Lactate dehydrogenase	Monocytes	
Lipase		
Gamma-glutamyl transferase		
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.

In order for the subject to receive inhaled study drug on Day 1, clinical laboratory assessments from the Screening Visit will have no clinically significant findings that preclude participation in the study, as judged by the investigator.

Pregnancy (beta-human chorionic gonadotropin [β-HCG]) 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 3-1, Table 3-2, and Table 3-3. The urine pregnancy test on Day 1, Day 57, and Day 85 must be confirmed to be negative before the first dose of study drug in the corresponding Treatment Period.

If a urine pregnancy test is positive, all study drug dosing will stop 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 discontinued from study drug as discussed in Section 11.6.5.2. If a pregnancy test is positive, the procedures outlined in Section 11.6.5.2 will be followed.

FSH (Screening Visit 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.

PCD Genotype: PCD genotyping will be performed during the Screening Period.

Specific instructions will be provided in the Study Reference Manual. Unless a confirmed PCD genotype is an inclusion criterion for a particular subject, the genotype result is not required in order for randomization to occur. If a confirmed PCD genotype is required for randomization, enough time should be given between collection of the sample and the Day 1 Visit to allow results to be received.

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

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

11.6.2.1 Hyperkalemia

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, study drug should be interrupted until the serum and plasma potassium are 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 Parion medical monitor or authorized designee. Subjects in whom treatment is discontinued for elevated potassium should have their potassium levels monitored closely until levels normalize or return to baseline.

11.6.2.2 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 within 48 to 72 hours of the initial finding, and have subsequent close monitoring of ALT and AST levels, as clinically indicated.

Study drug administration must be interrupted immediately and the Parion medical monitor must be notified if the following criterion is met:

- ALT or AST levels >5 × ULN

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

If criteria for study drug interruption is met and no convincing alternative etiology (e.g., acetaminophen use, viral hepatitis, alcohol ingestion) for the elevated ALT or AST levels are identified, regardless of whether the levels have improved, the subject must be discontinued from the study, in consultation with the Parion medical monitor (Section 9.5). An ETT Visit should be scheduled as soon as possible. Subjects discontinued for elevated ALT or AST levels should be followed until their levels normalize or return to baseline.

If a convincing alternative etiology is identified for the ALT and/or AST elevation, study drug may be resumed when both laboratory values return to baseline or are ≤2 × ULN, whichever is higher, after approval by the Parion medical monitor.

Upon resumption of study drug, ALT and/or AST must be assessed weekly for the shorter of:

- 4 weeks
- 1 week following the last dose of study drug, if ALT and/or AST levels have returned to baseline or ≤2 × ULN

Upon resumption of study drug, ALT and/or ALT levels must be assessed weekly for 4 weeks. If a repeat elevation of >5 × ULN occurs within 4 weeks of rechallenge with study drug, then study drug must be discontinued, regardless of the presumed etiology.

11.6.3 Physical Examinations and Vital Signs

A complete physical examination will be performed at the Screening Visit, Day 1, Day 29, Day 57, Day 85, Day 113, and ETT visits. At the Day 15, Day 71 and Day 99 visits (if completed), an abbreviated physical examination will be done. The complete physical examination will include the following components: HEENT (head, eyes, ears, nose, and throat), neck, chest and chest auscultation, cardiovascular, abdomen, skin, and musculoskeletal. The abbreviated physical examination will include the following components: HEENT, neck, chest auscultation, cardiovascular, and skin. Both the full and abbreviated physical examinations will exclude rectal and genitourinary examinations (see Table 3-1, Table 3-2, and Table 3-3).

After the Screening Visit, any clinically significant abnormal findings in physical examinations will be reported as AEs.

Vital signs include blood pressure (systolic and diastolic), body temperature, pulse rate (beats per minute), respiratory rate (breaths per minute), and pulse oximetry. These will be assessed

following at least a 5-minute rest in a sitting or supine position. After the Screening Visit, clinically significant abnormal findings in vital signs will be reported as AEs.

11.6.4 Electrocardiograms

Twelve-lead ECGs will be performed using a machine with printout according to the Schedule of Assessments (Table 3-1, Table 3-2, and Table 3-3). Additional 12-lead ECGs will be performed at any other time if clinically indicated. The performance of all ECGs will adhere to the following guidelines:

- The subject will be instructed to rest in a sitting or supine position for at least 5 minutes before having an ECG performed.
- Prior to placing ECG leads, the record will be reviewed for the presence of dextrocardia. Subjects with dextrocardia will have all ECG limb and chest (V) leads reversed.

The ECG traces will be manually read at the study site at the Screening Visit, Day 1, Day 15 (if a visit is conducted), Day 29, Day 57, Day 71 (if a visit is conducted), Day 85, Day 99 (if a visit is conducted), Day 113, and the ETT 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 (taking into consideration anticipated abnormalities in subjects with dextrocardia) occurring during the study through the Day 113 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 increases 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 the QTcF value remains above the threshold value on the repeat ECG measurement with no identified alternative etiology for the increased QTcF, then study drug should not be administered on that day and must be immediately interrupted. An ECG should be repeated within 48 to 72 hours to monitor the QTcF interval. Discussion with the Parion medical monitor must occur to determine whether study drug may be resumed or whether discontinuation from study drug treatment is indicated.

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

11.6.5 Contraception and Pregnancy

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

Ivacaftor did not show any effect in reproductive toxicology studies, including rat fertility, rat and rabbit embryo-fetal development, and rat peri/post-natal reproduction toxicity studies (refer to the Ivacaftor Investigator's Brochure).

[redacted] Results suggested that the clinical effects of the oral contraceptive would not likely be adversely impacted by coadministration with ivacaftor. Therefore, hormonal contraceptives are one acceptable means of contraception for female subjects of childbearing potential in this study.

11.6.5.1 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 must 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, post-ovulation 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 for male subjects and their female (non-study) partners, and for female subjects and their male (non-study) partners:

Table 11-2 Acceptable Methods of Contraception

• 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.

Important notes:

- Local requirements may prohibit the use of some of these acceptable methods listed above. Please contact the Parion 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 11-2.
- 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 Parion medical monitor on an individual basis.

11.6.5.2 Pregnancy

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

All pregnancies occurring during the study or within 90 days after discontinuation of study drug must be followed until resolution (i.e., birth or voluntary or spontaneous termination of the pregnancy). Any subject found to be pregnant at any time during the study will be withdrawn from the study immediately. Any pregnancy outcome that meets the criteria for an SAE will be reported as an SAE.

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

If confirmed to be on active drug, the subject or partner will be followed until the end of the pregnancy and the infant will be followed for 1 year after the birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

12 STATISTICAL AND ANALYTICAL PLANS

Parion Sciences or its designee will analyze the safety and efficacy data.

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

12.1 Sample Size and Power

Part A

The primary efficacy objective of Part A of this study is to evaluate the efficacy of VX-371 with and without HS in subjects ≥12 years of age with PCD. For efficacy analysis, the statistical inferences will be based on change from study baseline. The null hypotheses to be tested are that the mean absolute change from study baseline in $ppFEV_1$ after 28 days of treatment is the same

for 1) VX-371 in HS versus placebo; 2) VX-371 versus placebo; and 3) VX-371 in HS versus HS alone.

To have a feasible sample size and study duration, a crossover design has been proposed for Part A of this study. Assuming an SD of 7 percentage points, 50 subjects each for Treatment Sequence 1 and Treatment Sequence 2 are needed to have approximately 81% power to detect a 3-percentage point treatment difference in the mean absolute change in $ppFEV_1$ from study baseline, after 28 days of treatment between VX-371 + HS and HS alone. Part A of the study will have approximately 87% power to detect a 4-percentage point change from baseline, after 28 days of treatment in $ppFEV_1$ between VX-371 + HS and placebo. The power to detect a 3-percentage point difference between VX-371 and placebo is about 51%. The sample size estimate was based on 10000 simulation runs with an incomplete block design assuming no dropouts. In the simulation, the correlation between responses to the 2 treatments within a subject was assumed to be 0. Furthermore, a 2-sided significance level of 0.05 was used in the sample size determination with no multiplicity adjustment. The sample size also takes into consideration an assumed dropout rate of 10%.

Part A of the study will enroll approximately 150 subjects. However, as no therapeutic intervention study has previously been completed in PCD patients, the ability to enroll all 150 subjects is uncertain. Enrollment of less than 150 subjects will still provide useful information and could demonstrate an important difference between treatments. Enrollment into Part A will continue until approximately 150 subjects are randomized or the enrollment rate drops, despite suitable interventions, such that the planned enrollment cannot be achieved.

Part B

No formal sample size calculation was performed. All subjects who completed the assigned treatment in Part A and who meet the eligibility criteria for Part B will be offered enrollment in Part B.

12.2 Analysis Sets

Assignment of subjects to analysis sets will be done before the clinical database lock for the study.

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

Part A

The Part A Full Analysis Set (FAS) is defined as all randomized subjects who have received at least 1 dose of study drug in Part A. The Part A FAS is to be used in Part A efficacy analyses in which subjects will be analyzed according to the treatment to which they were assigned or background data summary according to the treatment sequence to which they were randomized in Part A. All analyses of background data and efficacy data in Part A will be based on the Part A FAS. In efficacy analyses, data for a period will be used provided that the subject received at least 1 dose of study drug in the Treatment Period.

The Part A Safety Set is defined as all subjects who received at least 1 dose of study drug in Part A. The Part A Safety Set is to be used for all Part A safety analyses in which subjects will be analyzed according to the treatment they received in each period of Part A. In safety analyses,

data for a period will be used provided that the subject received at least 1 dose of study drug in that Treatment Period.

Part B

The Part B FAS is defined as all subjects randomized in Part A and enrolled in Part B and who have received at least 1 dose of study drug in Part B. The Part B FAS is to be used in Part B efficacy analyses in which subjects will be analyzed according to the treatment as enrolled in Part B, which is ivacaftor plus the same treatment as assigned in Part A Treatment Period 2. All analyses of background data and efficacy data in Part B will be based on the Part B FAS.

The Part B Safety Set is defined as all subjects who received at least 1 dose of study drug in Part B. The Part B Safety Set is to be used for all Part B safety analyses in which subjects will be analyzed according to the treatment as enrolled in Part B, which is ivacaftor plus the same treatment as assigned in Part A Treatment Period 2.

12.3 Statistical Analysis

12.3.1 General Considerations

All individual subject data for those randomized or exposed to 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, 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 Period

Treatment-Emergent Period for Part A Treatment Period 1:

- For subjects who prematurely discontinue treatment in Part A Treatment Period 1, the Treatment-Emergent Period will be defined as the interval that occurs on or after first dose of Treatment Period 1 and up to 28 days after the last dose in Treatment Period 1.
- For subjects who continue into Treatment Period 2, the treatment emergent period will be defined as the interval that occurs on or after first dose of study drug in Treatment Period 1 and before first dose of study drug in Treatment Period 2.

Treatment-Emergent Period for Part A Treatment Period 2:

- For subjects who prematurely discontinue treatment in Treatment Period 2, the treatment-emergent period will be defined as the interval that occurs on or after first dose of study drug in Treatment Period 2 and up to 28 days after the last dose in Treatment Period 2.
- For subjects who complete Treatment Period 2, the treatment-emergent period will be defined as the interval that occurs on or after first dose of Treatment Period 2 and before first dose of Part B (Treatment Period 3).

Treatment-Emergent Period for Part B Treatment Period 3:

For subjects who receive treatment in Part B, the treatment-emergent period will be defined as the interval that occurs on or after first dose of study drug in Part B until the end of study.

Baseline: 2 types of baselines will be defined for Part A. The **study baseline** is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug. The definition will be applied to all demographics, background, and baseline characteristics and also efficacy data analysis, including the primary endpoint analysis. The **period baseline** is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug in each Treatment Period. For Part A Treatment Period 2, the period baseline should be from an assessment measured after the last dose for Treatment Period 1. This definition will be applied to all safety data analysis. This definition will be applied to all safety data analysis in Part A and Part B.

For Part B, 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 study drug (i.e., same baseline as for Part A). The Part B baseline is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug in Part B.

Change/Absolute Change from Study Baseline in Part A and Part B will be calculated as:

post-baseline value - study baseline value

Change/Absolute Change from Period Baseline in Part A and Part B will be calculated as:

post-baseline value - period baseline value

Change/Absolute Change from Part B Baseline will be calculated as:

post-baseline value - Part B 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 (e.g., medical history) will be summarized. Additionally, all subject data will be presented in subject data listings. All Part A summaries will be based on the Part A FAS and all Part B summaries will be based on the Part B 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

Part A

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

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

- Continued study in Part B
- Did not enroll in Part B

- Prematurely discontinued the study in Part A and the reasons for discontinuation

Part B

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

- Completed Part B study drug treatment
- Prematurely discontinued Part B study drug treatment and the reasons for discontinuation
- Completed study in Part B
- Prematurely discontinued the study in Part B and the reasons for discontinuation

12.3.2.2 Demographics and Baseline Characteristics

Demographic, background (e.g., medical history), and baseline characteristics will be summarized by treatment sequence for Part A and Part B. Protocol deviations/violations will be provided as a subject data listing only. Important protocol deviations/violations will be summarized.

The following demographics and study baseline characteristics will be summarized by treatment sequence for Part A FAS and by treatment for Part B FAS, respectively: sex, race, ethnicity, age, weight, height, body mass index (BMI), region, and study baseline ppFEV$_1$.

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 study drug in Part A, regardless of when it ended.
Concomitant medication: medication continued or newly received during the Treatment-Emergent Period for Part A (Treatment Period 1 or Treatment Period 2), or Part B (Treatment Period 3).

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, Part A concomitant medications will be summarized by treatment based on the Part A FAS, and Part B concomitant medications will be summarized by treatment based on the Part B FAS.

12.3.2.4 Study Drug Exposure and Compliance

Part A

Exposure to study drug in Part A (i.e., duration of treatment) will be summarized by treatment for the Part A FAS in terms of duration of treatment a subject received (in days), defined as:

the last day of study drug - the first day of study drug + 1 within each Treatment Period. Half days will be counted if the first dose is administered in the afternoon and/or the last dose is administered in the morning.

Study drug compliance will be calculated for each Treatment Period of Part A as follows:

100 × [(Total number of vials dispensed – the total number of unused vials returned – the total number of vials reported as lost or wasted in a Treatment Period of Part A) / (Duration of study drug exposure in the corresponding Treatment Period of Part A times 2)].

Duration of treatment and study drug compliance in Part A will be summarized by descriptive summary statistics by treatment.

Part B

Exposure to study drug in Part B (i.e., duration of treatment) will be summarized by treatment for the Part B FAS in terms of duration of treatment a subject received (in days), defined as the last day of study drug minus the first day of study drug in Part B plus 1. Half days will be counted if the first dose is administered in the afternoon and/or the last dose is administered in the morning.

Study drug compliance will be calculated for each study drug in Part B as follows:

100 × [(Total number of doses dispensed – the total number of unused doses returned – the total number of doses reported as lost or wasted in Part B) / (Duration of study drug exposure in Part B times 2)].

Duration of treatment and study drug compliance in Part B will be summarized by descriptive summary statistics by treatment.

12.3.3 Efficacy Analysis

For Part A efficacy analysis, the statistical inference will be based on change from study baseline. For Part B efficacy analysis, the statistical inference will be based on change from study baseline and change from Part B baseline.

All Part A efficacy summaries and analysis will be based on the Part A FAS and all Part B efficacy summaries and analysis will be based on the Part B FAS unless otherwise specified.

12.3.3.1 Analysis of Primary Efficacy Variables

Part A

The primary efficacy endpoint for Part A is the absolute change in $ppFEV_1$ from study baseline, after 28 days of treatment in each Treatment Period of Part A.

The null hypotheses to be tested are that the mean absolute change from study baseline in $ppFEV_1$ after 28 days of treatment is the same for 1) VX-371 in HS versus placebo; 2) VX-371 versus placebo; and 3) VX-371 in 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 $ppFEV_1$ after 28 days of treatment as the dependent variable, treatment and period as fixed effects, and subject as a random effect. The within-subject covariance will be assumed to have the compound symmetry (CS) structure. Denominator degrees of freedom for the F-test for fixed effects will be estimated using the Kenward-Roger approximation.[32] 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. There will be no adjustment for multiplicity. Similarly, the estimated between-treatment differences along with the corresponding 95% CI and 2-sided *P* values will be presented.

[redacted]

Part B

For the Part B primary efficacy endpoints, absolute change in $ppFEV_1$ from study baseline and from Part B baseline, after 28 days of treatment in Part B, and descriptive summary statistics (n, mean, SD, SE, median, minimum, and maximum) will be provided.

The within-group *P* value and the 95% confidence interval based on normal approximation will be provided for absolute change in $ppFEV_1$

- from study baseline, after 28 days of treatment in Part B
- from Part B baseline, after 28 days of treatment in Part B

12.3.3.2 Analysis of Secondary Efficacy Variables

Part A

For the Part A secondary efficacy endpoint, the primary analysis will be based on change from study baseline.

- Change in quality of life score as measured by the QOL-PCD after 28 days of treatment in Part A
- Change in the SGRQ after 28 days of treatment in Part A

Analysis of the change in QOL-PCD and SGRQ will be similar to that of the primary analysis of the Part A primary efficacy endpoint.

Part B

For the Part B secondary efficacy endpoint, the primary analysis will be based on change from study baseline as well as change from Part B baseline.

- Change in quality of life score as measured by the QOL-PCD after 28 days of treatment in Part B
- Change in the SGRQ after 28 days of treatment in Part B

Analysis of the change in QOL-PCD and SGRQ will be similar to that of the primary analysis of the Part B primary efficacy endpoints.

[redacted]

12.3.4 Safety Analysis

All safety analyses will be based on the set of data associated with the treatment emergent period for Part A Treatment Period 1, the treatment emergent period for Part A Treatment Period 2, and the treatment emergent period for Part B (Treatment Period 3). Part A safety analyses will be based on the Part A Safety Set. The summaries will be by treatment received in Part A. Part B safety analyses will be based on the Part B Safety Set. The summaries will be by treatment received in Part B.

For safety analysis, the period baseline will be used for Part A and the Part B baseline will be used for Part B.

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

The overall safety profile of 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., urine, serum and plasma chemistry, and hematology)
- ECG results
- Spirometry
- Vital signs
- Pulse oximetry

12.3.4.1 Adverse Events

For analysis purposes, AEs will be classified as pre-treatment AEs or TEAEs, defined as follows:

Pre-treatment AEs: Any AEs that started before the initial dosing of study drug.

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

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 of Part A, the start date will be imputed to the first dosing date of Part A and the AE assigned to the treatment in Part A Treatment Period 1. 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 of Part B, the start date will be imputed to the first dosing date of Part B and the AE assigned to the treatment in Part A Treatment Period 1. Therefore, for AEs with missing or partial start date, it is possible the AE is considered treatment-emergent in both Part A Treatment Period 1 and Part B.

Part A and Part B

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

- All TEAEs
- TEAEs by worst/highest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- TEAEs leading to death
- Frequently reported TEAEs

Summaries will be presented by treatment 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 AEs will be provided separately for Part A and Part B.

All AEs, including pre-treatment AEs, will be presented in individual subject data listings.

12.3.4.2 Clinical Laboratory Assessments

Part A

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

The number and percentage of subjects with at least 1 laboratory abnormality meeting the threshold analysis criteria during the Part A Treatment Emergent Period will be summarized by treatment. The threshold analysis criteria will be provided in the SAP.

Part B

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

The number and percentage of subjects with at least 1 laboratory abnormality meeting the threshold analysis criteria during the Part B treatment emergent period will be summarized by treatment. The threshold analysis criteria will be provided in the SAP.

Part A and Part B

Results of urinalysis and serum/urine pregnancy tests 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.

12.3.4.3 Electrocardiogram

Part A and Part B

A summary of raw values and change from Part A and Part B period baseline values will be provided by treatment at each scheduled visit for the following ECG measurements: heart rate, QRS duration, PR, and QTcF intervals. The number and percentage of subjects with at least 1 threshold analysis event during the treatment emergent period will also be tabulated. The threshold analysis criteria will be provided in the SAP.

12.3.4.4 Vital Signs

Part A and Part B

The summary of raw values and change from Part A and Part B period baseline values for the following vital signs will be presented by treatment at each scheduled time point: systolic and

diastolic blood pressure (mm Hg), body temperature, pulse rate (beats per minute), and respiratory rate (breaths per minute). The number and percentage of subjects with at least 1 threshold analysis event during the treatment emergent period will also be tabulated. The threshold analysis criteria will be provided in the SAP.

12.3.4.5 Physical Examination

For Parts A and B, physical examination results will be presented in individual subject data listings only. Clinically relevant results identified after the Screening Visit will be reported as AEs.

12.3.4.6 Spirometry

Part A

Spirometry data in Part A will be summarized based on the Part A Safety Set. This will include the number and percentage of subjects at each scheduled time point with predefined decreases in $ppFEV_1/FEV_1$ relative to Part A period baseline value.

Part B

Spirometry data in Part B will be summarized based on the Part B Safety Set. This will include the number and percentage of subjects at each scheduled time point with predefined decreases in $ppFEV_1/FEV_1$ relative to Part B baseline value.

12.3.4.7 Other Safety Analysis

12.3.4.7.1 Pulse Oximetry

Part A

The summary of raw values and change from Part A period baseline values will be presented by treatment at each scheduled time point for the percent of oxygen saturation by pulse oximetry.

The number and percentage of subjects with shift changes from Part A period baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the Part A treatment emergent period will be tabulated by treatment.

Part B

The summary of raw values and change from Part B baseline values will be presented by treatment at each scheduled time point for the percent of oxygen saturation by pulse oximetry.

The number and percentage of subjects with shift changes from Part B baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the Part B treatment emergent period will be tabulated by treatment.

12.3.5 Interim and IDMC Analyses

12.3.5.1 Interim Analysis

Not applicable

12.3.5.2 IDMC Analysis

An IDMC will be formed before study initiation. The IDMC's objectives and operational details will be defined in a separate document (IDMC charter), which will be finalized before the first

subject is screened. The IDMC will conduct regular planned safety reviews of study data as outlined in the IDMC charter.

[redacted]

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

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

- Concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention
- Discontinuation from the study

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

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time ICF is signed and study procedures have started until the following time points:

- For subjects who are not randomized until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Telephone Call: through the Safety Follow-up Telephone Call
- For subjects who Early Terminate from the study: through the Safety Follow-up Telephone Call

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

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

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and non-serious AEs. The guidance available at the following website will be consulted: 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 2012). 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 re-appeared on re-exposure to the investigational study drug.
Possibly related	There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
Unlikely related	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
Not related	The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the study subject's medical record).

13.1.1.6 Study Drug Action Taken

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

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

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

13.1.1.7 Adverse Event Outcome

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

Table 13-4 Classifications for Outcome of an AE

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

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

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

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

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the subject signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure will not be considered to

indicate an SAE, unless an AE caused the hospitalization or procedure to be rescheduled sooner or to be prolonged relative to what was planned. In addition, hospitalizations clearly not associated with an AE (e.g. social hospitalization for purposes of respite care) will not be considered to indicate an SAE.

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

13.1.2.2 Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through the Follow-up Visit, 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 Call and are considered related to study drug(s) will be reported to Vertex GPS and Parion Sciences **within 24 hours**.

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

13.1.2.3 Reporting Serious Adverse Events

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

Please send completed SAE Forms to Vertex GPS and Parion Sciences at the following:

Vertex GPS
Email: [redacted]
Fax: [redacted]
Contact Telephone: [redacted]

Parion Sciences
Email: [redacted]

13.1.2.4 Expedited Reporting and Investigator Safety Letters

Vertex, as the IND sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities and Parion Sciences. Parion Sciences will report these events to all participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, Parion Sciences, the study manager, or authorized designee, will be responsible for the submission of safety letters investigators and 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 use 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 either:
  - 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 prior to the return of the device by the subject, must be reported to Vertex GPS and Parion Sciences 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 and Parion Sciences at the following:

Vertex GPS
Email: [redacted]
Fax: [redacted]
Contact Telephone: [redacted]

Parion Sciences
Email: [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 IND sponsor, is responsible for evaluating and reporting unanticipated adverse device effects (UADEs) involving the investigational device used in this study to all regulatory authorities. Parion Sciences will report these events to all participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, Parion Sciences, the study manager, 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 Parion Sciences, the study manager, or authorized designee, 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 pediatric subjects (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 Parion Sciences or its designee.

13.2.3 Investigator Compliance

No modifications to the protocol will be made without the approval of both the investigator and Parion Sciences. 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. Parion Sciences 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 Parion Sciences to discuss the planned course of action. If possible, contact will be made before the implementation of any changes. Any departures from protocol will be fully documented in the source documentation and in a protocol deviation log.

13.2.4 Access to Records

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

13.2.5 Subject Privacy

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

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, Parion Sciences, 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 Parion Sciences will be notified.

13.2.7 Study Termination

At any time, Parion Sciences 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

Parion Sciences 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 randomized subject will be entered into a CRF by study site personnel using a secure, validated web-based electronic data capture (EDC) application. Parion Sciences 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 Parion Sciences 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 Parion Sciences or its designee. Monitoring will be done by personal visits from a representative of Parion Sciences, 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

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

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

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

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

Parion Sciences 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

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.

14 REFERENCES

1 Knowles MR, Daniels LA, Davis SD, Zariwala MA, Leigh MW. Primary ciliary dyskinesia. Recent advances in diagnostics, genetics, and characterization of clinical disease. Am J Respir Crit Care Med. 2013;188(8):913-22.

2 Halbert SA, Patton DL, Zarutskie PW, Soules MR. Function and structure of cilia in the fallopian tube of an infertile woman with Kartagener's syndrome. Hum Reprod. 1997;12(1):55-8.

3 Noone PG, Leigh MW, Sannuti A, Minnix SL, Carson JL, Hazucha M, et.al. Primary ciliary dyskinesia: diagnostic and phenotypic features. Am J Respir Crit Care Med. 2004; 169(4):459-67.

4 Leigh MW, Hazucha MJ, Chawla KK, Baker BR, Shapiro AJ, Brown DE, et.al. Standardizing nasal nitric oxide measurement as a test for primary ciliary dyskinesia. Ann Am Thorac Soc. 2013;10(6):574-81.

5 Afzelius BA. A human syndrome caused by immotile cilia. Science. 1976;193(4250):317-9.

6 Lie H, Zariwala MA, Helms C, Bowcock AM, Carson JL, Brown, DE, et. al. Primary ciliary dyskinesia in Amish communities. J Pediatr. 2010;156(6):1023-5.

7 O'Callaghan C, Chetcuti P, Moya E. High prevalence of primary ciliary dyskinesia in a British Asian population. Arch Dis Child. 2010;95(1):51-2.

8 Ferkol TW, Puffenberger EG, Lie H, Helms C, Strauss KA, Bowcock A, et al. Primary ciliary dyskinesia-causing mutations in Amish and Mennonite communities. J Pediatr. 2013;163(2):383-7.

9 Fedick AM, Jalas C, Treff NR, Knowles MR, Zariwala MA. Carrier frequencies of eleven mutations in eight genes associated with primary ciliary dyskinesia in the Ashkenazi Jewish population. Mol Genet Genomic Med. 2015;3(2):137-42.

10 Zariwala MA, Omran H, Ferkol TW. The emerging genetics of primary ciliary dyskinesia. Proc Am Thorac Soc. 2011;8(5):430-3.

11 Davis SD, Ferkol TW, Rosenfeld M, Lee HS, Dell SD, Sagel SD, et al. Clinical features of childhood primary ciliary dyskinesia by genotype and ultrastructural phenotype. Am J Respir Crit Care Med. 2015;191(3):316-24.

12 Daniels MLA, Noone PG. Genetics, diagnosis and future treatment strategies for primary ciliary dyskinesia. Expert Opinion on Orphan Drugs. 2015;3(1):31-44.

13 Button B, Okada SF, Frederick CB, Thelin WR, and Boucher RC. Mechanosensitive ATP release maintains proper mucus hydration of airways. Sci Signal. 2013; 6(279): ra46.

14 Bush A, Payne D, Pike S, Jenkins G, Henke MO, and Rubin BK. Mucus properties in children with primary ciliary dyskinesia: comparison with cystic fibrosis. Chest. 2006;129(1):118-23.

[redacted]

16 Button B, Cai LH, Ehre C, Kesimer M, Hill DB, Sheehan, et.al. A periciliary brush promotes the lung health by separating the mucus layer from airway epithelia. Science. 2012;337(6097):937-41.

17 Ehre C, Button B, Randell SH, Boucher RC. Increased mucin expression, mucus accumulation, and mucus adhesion in CF lungs. Pediatr Pulmonol. 2009;S32:68.

18 Cai L, Button B, Boucher RC, Rubinstein, M. Role of mucus adhesion and cohesion in mucus clearance. Pediatr Pulmonol. 2012;S35:141.

19 Kim CS, Rodriguez CR, Eldridge MA, Sackner MA. Criteria for mucus transport in the airways by two-phase gas-liquid flow mechanism. J Appl Physiol. 1986;60(3): 901-907.

20 Button B, Grubb BR. Cilia-independent gas-liquid transport: A novel mechanism of mucus clearance. Pediatr Pulmonol. 2010;S33:165.

21 Shenoy SK, Goodell HP, Carson JL, Mitran S, Dennis RG, Button B. Airflow-mediated mucus transport: a novel form of clearance. Pediatr Pulmonol. 2013;S36:183.

22 Van Goor F, Hadida S, Grootenhuis PD, Burton B, Cao D, Turnbull A, Singh A, Joubran J, Hazlewood A, Zhou J, McCartney J, Arumugam V,Decker C, Yang J, Young C, Olson ER, Wine JJ, Frizzell RA, Ashlock M, Negulescu P. Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. Proc Natl Acad Sci U S A. 2009;106(44):18825-30.

[redacted]

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

25 Dell SD, Leigh MW, Lucas JS, Ferkol TW, Knowles MR, Alpern A, et.al. Primary ciliary dyskinesia: first health-related quality of life measures for pediatric patients. Ann Am Thorac Soc. 2016;13(10):1726-35.

26 Lucas JS, Behan L, Galvin AD, Alpern A, Morris AM, Carroll MP, et.al. A quality-of-life measure for adults with primary ciliary dyskinesia: QOL-PCD. Eur Respir J. 2015;46(2):375-83.

27 St. George's University of London Health Status Research website. Available at: http://www.healthstatus.sgul.ac.uk/sgrq. Accessed 20 October 2015.

[redacted]

29 Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatr Pulmonol. 1976;58:259-63.

30 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.

31 Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et.al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.

32 Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 1997;53:983-97.

15 PROTOCOL SIGNATURE PAGES

15.1 Parion Signature Page

Protocol #: PS-G202	Version #: 6.0	Version Date 31 Oct 2016
Study Title: A Phase 2a, 2-part, Randomized, Double-blind, Placebo-controlled, Incomplete Block Crossover Study to Evaluate the Safety and Efficacy of VX-371 Solution for Inhalation With and Without Oral Ivacaftor in Subjects With Primary Ciliary Dyskinesia		

[redacted]

Parion Sciences Incorporated [redacted]

Vertex Pharmaceuticals Incorporated
Parion Sciences, Inc. [redacted]

15.2 Investigator Signature Page

Protocol #: PS-G202	Version #: 6.0	Version Date 31 Oct 2016
Study Title: A Phase 2a, 2-part, Randomized, Double-blind, Placebo-controlled, Incomplete Block Crossover Study to Evaluate the Safety and Efficacy of VX-371 Solution for Inhalation With and Without Oral Ivacaftor in Subjects With Primary Ciliary Dyskinesia		

I have read Protocol PS-G202, Version 6.0 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 Parion Sciences Incorporated (Parion Sciences) is confidential.

_____
Printed Name

_____ _____
Signature Date