Statistical Analysis Plan

[redacted]

Sponsor Name:	Parion Sciences Incorporated
Protocol Number and Title:	**PS-G202: 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**
Protocol Version and Date:	**Version 6.0 31Oct2016**
[redacted]	**1006696**
Author(s):	[redacted] Lead Biostatistician
SAP Version:	1.0
SAP Version Date:	24th July 2018

[redacted]

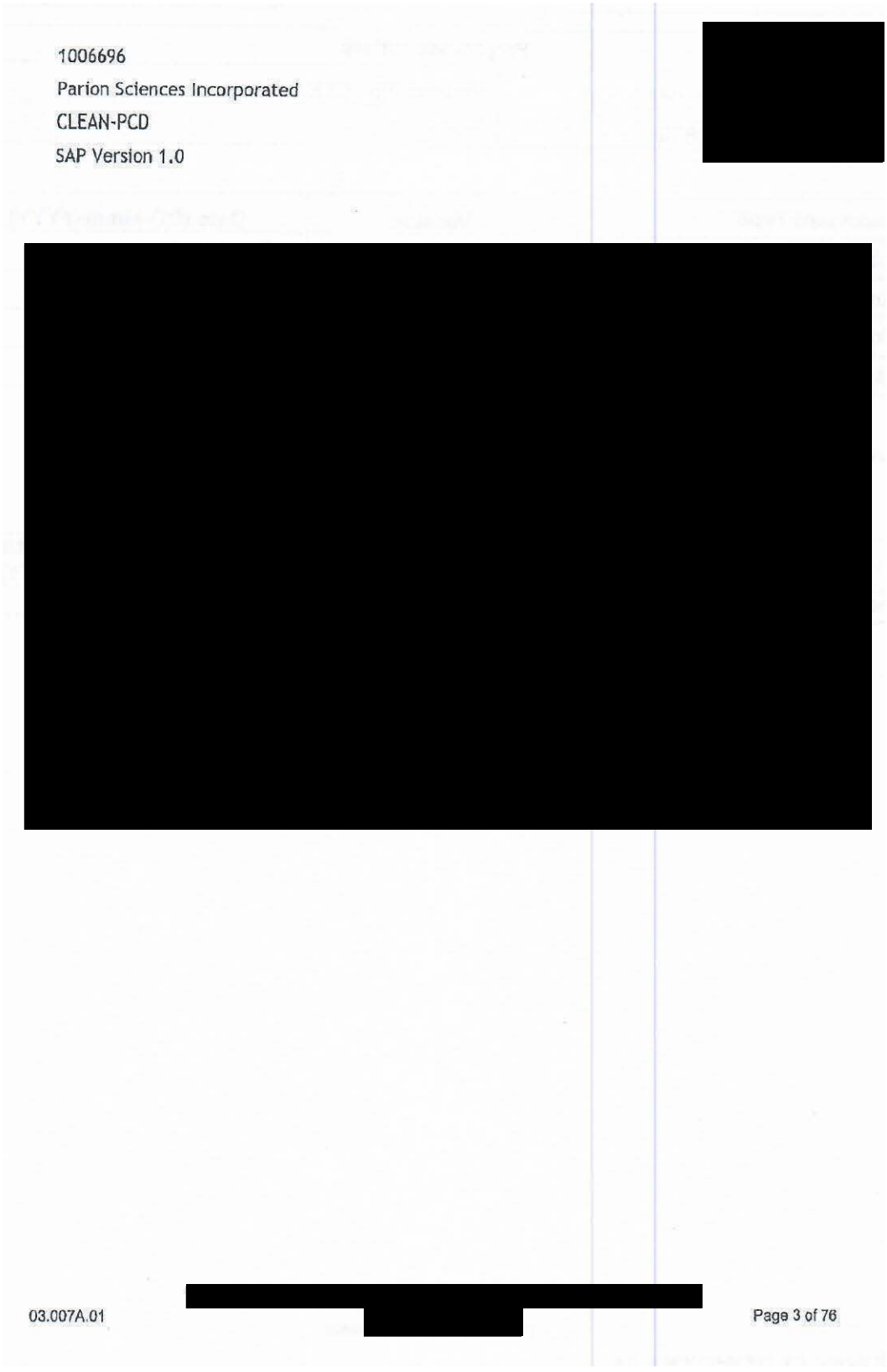
1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

Version: ___1.0_____ Version Date: ___24th Jul 2018_____

I confirm that I have reviewed this document and agree with the content.

[redacted]

03.007A.01 [redacted] Page 2 of 76


1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0
[redacted]
[redacted]
03.007A.01
[redacted]
Page 3 of 76

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

TABLE OF CONTENTS

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

1 GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
CM	Concomitant Medication
CS	Compound Symmetry
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EU	Europe
FAS	Full Analysis Set
$FEF_{25\%-75\%}$	Forced Midexpiratory Flow Rate
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
HS	Hypertonic Saline
IDMC	Independent Data Monitoring Committee
K+	Potassium
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
NA	North America
Na+	Sodium

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

Abbreviation	Description
PBO	Placebo
PCD	Primary Ciliary Dyskinesia
pp	Percentage Predicted
PT	Preferred Term
QTcF	Corrected QT Interval by Fridericia's Formula
[redacted]	[redacted]
PR	PR Interval, Segment
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
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SGRQ	St. George's Respiratory Questionnaire
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
TE	Treatment-Emergent
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
ULN	Upper Limit of Normal

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

2 PURPOSE

The purpose of this statistical analysis plan (SAP) is to describe the planned statistical analyses of efficacy endpoints and safety endpoints for the final analysis. The SAP clarifies that analysis of Part A and Part B data will be presented separately. [redacted]

2.1 RESPONSIBILITIES

[redacted] will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings.

2.2 TIMINGS OF ANALYSES

The primary analysis of safety and efficacy and pharmacokinetics is planned after all subjects complete all three treatment periods for this study or terminate early from any of the treatment periods during the study. Unless otherwise specified, the analysis includes all data collected in the database through the time of the database lock.

Periodic Independent Data Monitoring Committee Meetings (IDMC) have been held to monitor ongoing subject safety. The details of these analyses are specified in the IDMC charter and IDMC SAP. An unblinded team from [redacted] which is independent from the study team performed the analyses to maintain the blinding of the study.

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

3 STUDY OBJECTIVES

3.1 PART A

3.1.1 Primary Objective

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.

3.1.2 Secondary Objective

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.

3.2 PART B

3.2.1 Primary Objective

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.

3.2.2 Secondary Objective

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.

3.3 BRIEF DESCRIPTION

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 a 2:2:1:1 ratio in Part A, stratifying for percent predicted forced expiratory volume in 1 second (ppFEV1) severity (<70 or ≥70) as described in Table 1. 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 1.

Table 1. Study PS-G202 Treatment Sequences

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

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

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.

3.4 SUBJECT SELECTION

Protocol V6.0 section 9 specifies the details of eligibility criteria.

3.5 DETERMINATION OF SAMPLE SIZE

3.5.1 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 ppFEV1 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 ppFEV1 from study baseline, after 28 days of treatment between VX-371 + HS

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

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 ppFEV1 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.

3.5.2 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.

3.6 TREATMENT ASSIGNMENT & BLINDING

Approximately 150 subjects will be randomized to 1 of 4 treatment sequences in double-blind fashion 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 ppFEV1 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 based a centralized randomization scheme. The randomization code will be produced by [redacted]. 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 [redacted] biostatistician responsible for the IDMC analyses to maintain the study blind throughout the course of the study until the final database lock.

There is no randomization in Part B. Subjects will remain in the same treatment as in

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

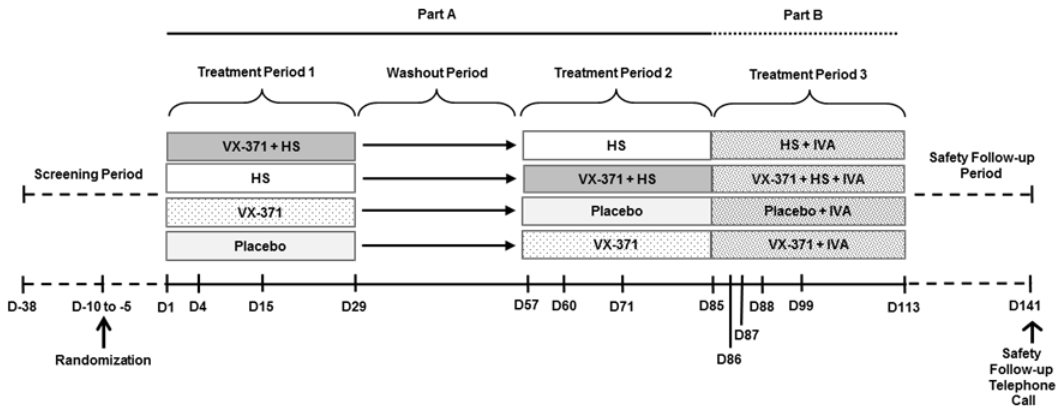
Treatment Period 2 of Part A and will also receive open-label oral ivacaftor.

3.7 ADMINISTRATION OF STUDY MEDICATION

Protocol V6.0 section 10 specifies the details of study drug administration.

3.8 STUDY PROCEDURES AND FLOWCHART

A schematic of the study design is provided below:



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)

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

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.

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.

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.

Schedules of Assessments are shown in Appendix IV Table 5, Table 6 and Table 7

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

4 ENDPOINTS

4.1 PART A

4.1.1 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 ppFEV1 from study baseline, after 28 days of treatment in Part A

4.1.2 Secondary Endpoints

- Change in QOL score as measured by the Quality of Life-PCD Questionnaire (QOL-PCD) and the St. George's Respiratory Questionnaire (SGRQ)[1] from study baseline, after 28 days of treatment in Part A

[redacted]

4.2 PART B

4.2.1 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

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

- Absolute change in ppFEV1, from study baseline and Part B baseline after 28 days of treatment in Part B

4.2.2 Secondary Endpoints

- 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]

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

5 ANALYSIS SETS

5.1 SCREENED SUBJECTS

Screened subject for Part A is defined as any subject who signed the study specific informed consent and had at least one study procedure performed during the screening period.

5.2 ALL SUBJECTS SET

5.2.1 Part A

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

5.2.2 Part B

The Part B All Subjects Set is defined as all subjects who enrolled (signed the Part B informed consent) in Part B.

5.3 FULL ANALYSIS SET

5.3.1 Part A

The Part A Full Analysis Set (FAS) is defined as all randomized subjects who received at least 1 dose of study drug in Part A and had a confirmed diagnosis of PCD. The Part A FAS subjects will be analyzed according to the treatment to which they were assigned in each period of Part A. Data for a period will be used provided that the subject received at least 1 dose of study drug in that Treatment Period.

5.3.2 Part B

The Part B FAS is defined as all subjects who had a confirmed diagnosis of PCD and received at least 1 dose of ivacaftor in Part B. The Part B FAS 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.

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

5.4 SAFETY SET

5.4.1 Part A

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 subjects will be analyzed according to the treatment they received in each period of Part A. Data for a period will be used provided that the subject received at least 1 dose of study drug in that Treatment Period.

5.4.2 Part B

The Part B Safety Set is defined as all subjects who received at least 1 dose of ivacaftor in Part B. The Part B Safety Set subjects will be analyzed according to the treatment they actually received in Part B.

5.5 IMPORTANT PROTOCOL DEVIATIONS

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. IPD rules will be developed and finalized prior to the database lock.

The protocol deviations that should be considered as potential IPDs include, but are not limited to:

- Subject was randomized despite the violation of inclusion/exclusion criteria
- Subject was less than 80% compliant with study drug
- Subject received prohibited concomitant medications
- Subject received the wrong treatment or incorrect doses
- Subject remained in the study despite meeting withdrawal criteria

Occurrence of any of these events should be considered as potential IPDs, but a blinded team should categorize them as IPDs only if they have the potential to significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

IPDs (from the clinical database or from the site deviation log) will be summarized descriptively based on the FAS and presented by treatment sequence in Part A and by treatment in Part B. Additionally, IPDs will be provided in an individual subject data listing.

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

6 GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1 GENERAL METHODS

All analyses will be implemented using SAS Version 9.3 or higher. Data summaries will be presented by treatment . All data will be listed.

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

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

General rules of precision are as follows:

- Minimum and maximum values will be reported with the same precision as the reported measurement unless otherwise specified. For the calculated variables, two decimal places will be reported.
- Mean and median will be reported to 1 greater decimal place than the precision of the reported measurement unless otherwise specified.
- Standard deviation and standard error (to indicate standard error of an estimate from a statistical model) will be reported to 1 greater decimal place than the corresponding mean.
- Report p-values to 4 decimal places; report as "<0.0001", when applicable.
- In general, the precision of mean, LS Mean, and 95% CI for a variable is the same, unless otherwise specified.

6.2 KEY DEFINITIONS

6.2.1 Baseline

Two types of baseline 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 in the study. The definition will be applied to all demographics, background, and baseline characteristics and efficacy data analyses, including the primary endpoint analysis. The **period baseline** is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in each Treatment Period. For Part A Treatment Period 2, the period

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

baseline will be the first assessment measured after treatment-emergent (TE) period for Period 1. This definition will be applied to all safety data analyses.

For spirometry analysis in Part A, if Period 1 day 1 pre-dose data is not available, data collected at the screening visit before the test HS dose will be used as Period 1 baseline or study baseline instead of the last non-missing screening visit after the test HS dose.

For weight, height and BMI, study baseline and Period 1 baseline will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before or on the day of the first dose of study drug in Part A, Period 1. Similarly, Period 2 baseline will consider the most recent non-missing measurement (scheduled or unscheduled) collected after the TE period for Period 1 and before or on the day of first dose of study drug in Part A, Period 2.

For SGRQ and QOL-PCD, study baseline will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before or on the day of the first dose of study drug in Part A, Period 1.

For Part B, two types of baseline, study baseline and Part B baseline, will be defined. The study baseline is defined the same as study baseline for Part A. The Part B baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of ivacaftor in Part B and after the last dose in Period 2.

- 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 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

For weight, height and BMI, SGRQ and QOL-PCD, Part B baseline will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before or on the day of the first dose of ivacaftor in Part B and after the last dose in Period 2.

6.2.2 Treatment Emergent Period

Treatment-emergent (TE) period for Part A Treatment Period 1:

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

- The Treatment-Emergent Period will correspond to the interval from the first dose date of Treatment Period 1 to 28 days after the last dose date of Treatment Period 1 or the date before the first dose date of Treatment Period 2 or the safety follow-up visit, whichever occurs earlier.

TE period for Part A Treatment Period 2:

- The treatment emergent period will correspond to the interval from the first dose date of Treatment Period 2 to 28 days after the last dose date of Treatment Period 2 or the date before the first dose date of Part B or the safety follow-up visit, whichever occurs earlier.

Treatment-Emergent Period for Part B:

- The treatment emergent period will correspond to the interval from the first dose date of study drug in Part B to 28 days after the last dose date of Part B or the safety follow-up visit, whichever occurs earlier.

6.3 MISSING DATA

Imputations for missing or partially missing start/end dates for prior/concomitant medications and adverse events are described in Appendix V.

Imputation for missing individual QOL-PCD scores is described in Appendix II.

No other imputations will be performed for missing data. Observed data will be used in the analyses.

6.4 VISIT WINDOWS

Visit windows can be found in Appendix VI

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

7 DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1 SUBJECT DISPOSITION AND WITHDRAWALS

Part A

The number of subjects in the following categories will be presented by treatment group:

- All Subjects Set (randomized or dosed)
- Randomized (defined as subjects who were assigned a treatment sequence but have not necessarily taken a dose of study drug).
- Randomized but not dosed
- Full Analysis Set (FAS)
- Safety Set

The number of subjects in the following categories will be presented by treatment group for each period (Period 1 and Period 2):

- Full Analysis Set (FAS)
- Safety Set

The number and percentage (based on Part A FAS) of subjects in each of the following disposition categories will be presented by treatment group for each period (Period 1 and Period 2):

- Completed treatment regimen
- Prematurely discontinued the treatment and the reasons for discontinuation
- Prematurely discontinued the study and the reasons for discontinuation

The number and percentage (based on the overall FAS) of subjects in each of the following disposition categories will be presented by treatment group:

- Completed treatment regimen in both periods
- Completed study in Part A
- Rolled-over to Part B

A listing of subjects who discontinued study or discontinued treatment regimen for Part A will be provided.

Part B

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

The number of subjects in the following categories will be presented by treatment group and overall:

- Full Analysis Set (FAS)
- Safety Set

The number and percentage (based on Part B FAS) of subjects in each of the following disposition categories will be presented by treatment group and overall:

- 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

A listing of subjects who discontinued study or discontinued treatment regimen for Part B will be provided.

7.2 SUBJECT SCREENED AND SCREEN FAILURE

Screen failure for Part A is defined as any screened subject who was not dosed with study drug.

Number of screened subjects and number and percentages of screen failures will be summarized, and all screen failures will be listed with their corresponding screen failure reason.

A listing for randomized but not dosed subjects (a subset of screen failure subjects) will be provided.

7.3 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized for Part A and Part B.

The following demographics and study baseline characteristics will be summarized by Period 1 treatment and Period 2 treatment for Part A FAS and overall, treatment for Part B FAS and overall: sex, child bearing potential, race, ethnicity, age at baseline, age (<18 years old), weight, height, body mass index (BMI), region (North America and Europe), study baseline ppFEV1, nNO measurement (nNO level 1 and nNO level 2), laterality defect, ciliary ultrastructure defect, and PCD genetic mutation.

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

In addition, Part B baseline characteristics will also be summarized based on Part B FAS by treatment group and overall, including age at Part B baseline, weight, height, BMI and ppFEV1.

7.4 MEDICAL HISTORY

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version: 18.1.

Medical history data will be summarized by Period 1 treatment and Period 2 treatment for Part A FAS and by treatment for Part B FAS.

7.5 MEDICATION

Medications will be coded using World Health Organization (WHO) DRUG dictionary, Version: WhoDrugDDEB2 201512 (ENG).

7.5.1 Prior Medication

Prior medication is defined as any medication that has a start date before the first dose of study drug in Part A, regardless of when it ended.

If the medication end date is before the date of first dose of study drug, then the medication will be summarized as prior medication regardless of whether the medication start date is missing or not.

Prior medications will be summarized by ATC level 1 and 2 term, preferred term (PT) and treatment for Part A and Part B separately.

7.5.2 Concomitant Medication

Concomitant medication is defined as any medication that is continued or newly received during the Treatment-Emergent (TE) period for Part A, or Part B.

A medication that starts/ends on or after the start date of the Treatment Emergent Period, up through and before the start date of the next Treatment Emergent Period, will be assigned to the treatment group associated with the current Treatment Emergent Period.

For the cases when Treatment Emergent Period 2 end of dosing is on the same day as the Treatment Emergent Period for Part B start of dosing date, any medication starting on the same day as the Treatment Emergent Period for Part B start of dosing date, will be assigned to the treatment in Period for Part B.

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

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 and it cannot be determined whether the medication was taken before initial dosing or concomitantly, it will be considered as prior and concomitant, and this medication will be assigned to all treatment groups.

If the start date of the medication is the same as the date of the first dose date of the study drug in Period 1, then the medication is classified as a concomitant medication and will be assigned to Period 1 treatment group.

Concomitant medications will be summarized by ATC level 1 and 2 term and preferred term (PT). 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.

7.5.3 Medication during Wash-out and Follow-up Period

The medication will also be summarized and listed for wash-out period and follow-up period overall. Washout Period will start on the day after the last dose date in Period 1 and end on the day before dosing in Period 2. Follow-up Period will start on the day after the last dose of study drug in the study.

7.6 STUDY DRUG EXPOSURE AND COMPLIANCE

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

- If a patient takes the first dose of study drug in the morning and the last dose of study drug in the afternoon, then exposure (days) will be defined as: last day of study drug – first day of study drug + 1
- If a patient takes the first dose of study drug in the morning and the last dose of study drug in the morning, then exposure (days) will be defined as: last day of study drug – first day of study drug + 0.5
- If a patient takes the first dose of study drug in the afternoon and the last dose of study drug in the morning, then exposure (days) will be defined as: last day of study drug – first day of study drug
- If a patient takes the first dose of study drug in the afternoon and the last dose of study drug in the afternoon, then exposure (days) will be defined as: last day of study drug – first day of study drug + 0.5

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

Study drug compliance will be summarized by treatment based on Part A FAS and Part B FAS. Study drug compliance will be calculated for each treatment 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) / (Duration of study drug exposure in the corresponding Treatment Period times 2)].

For Part B ivacaftor, compliance will be calculated as follows:

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

Duration of treatment and study drug compliance will be summarized by descriptive summary statistics by treatment. A separate categorical summary will be provided for the count and percent of subjects with the following compliance levels: <80% and >=80%.

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

8 EFFICACY

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. The change from study baseline will provide an assessment of the overall ivacaftor+VX-371 with and without HS effect. The change from Part B baseline will provide an assessment of additional effect of ivacaftor on top of the treatment in Part A treatment period 2 assuming that the effect of treatment in Part A treatment period 2 is stabilized by the time of ivacaftor treatment in Part B.

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

8.1 PRIMARY EFFICACY ENDPOINT AND ANALYSIS

Part A

The primary efficacy endpoint for Part A is the absolute change in ppFEV1 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 ppFEV1 after 28 days of treatment is the same for 1) VX-371 in HS versus placebo; 2) VX-371 versus placebo; 3) VX-371 in HS versus HS alone. The primary assessment of efficacy will be based on the comparison of 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 ppFEV1 after 28 days (Visit Day 29 for Period 1 and Day 85 for Period 2) of treatment as the dependent variable, treatment and period as fixed effects, study baseline as a covariate, 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. No imputation of missing data will be done.

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.

A sample SAS code is provided below:

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

[redacted]

Waterfall plot of the change from study baseline in ppFEV1 at Day 29 will be plotted by treatment group.

[redacted]

Summary statistics for the actual values and absolute changes from study baseline in pre-dose ppFEV1 will be summarized descriptively by treatment and visit based on Part A FAS.

In addition, the actual values and absolute changes at post-HS screening from pre-HS screening visit as well as actual values and absolute changes at Day 1 post-dose from Day 1 pre-dose in each period will be summarized based on Part A Safety Set and Part B Safety Set.

[redacted]

[redacted]

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

Part B

For the Part B primary efficacy endpoints, absolute changes in ppFEV1 from study baseline and from Part B baseline, after 28 days of treatment in Part B, descriptive summary statistics will be provided.

The absolute change from study baseline in ppFEV1 at Day 29 of Part B (Visit Day 113) will be analyzed using an Analysis of Covariance (ANCOVA) model with treatment as an independent variable and study baseline as well as treatment-by-study baseline interaction as covariate. The same model will be repeated using the Part B baseline instead. The LS means along with the 95% CIs and the within-treatment 2-sided P-values will be provided by treatment group. An overall estimate of the mean change across the treatment groups will also be provided with sample size for each treatment group as the weight.

Waterfall plot of the absolute change from study baseline and Part B baseline in ppFEV1 at Day 29 will be plotted by treatment group.

8.2 SECONDARY EFFICACY ENDPOINTS AND ANALYSES

Part A

SGRQ:

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

The SGRQ will have three domains (Symptoms, Activity, Impacts) and Total for age groups ≥ 16 [redacted]

SGRQ total score for [redacted] will be analyzed using similar analyses as described in Section 8.1 Part A including mixed effect model and waterfall plot. Note that the mixed effect model will use study baseline for ppFEV1 as a baseline covariate. [redacted]

The summary statistics for the actual values and absolute changes from study baseline will be obtained for SGRQ total score [redacted].

QOL-PCD:

The QOL-PCD [redacted] – adult version, [redacted] Subjects aged 18 years and older at Day 1 of Part A will complete the Adult version of the questionnaire themselves at all visits. [redacted]

The Lower Respiratory Symptoms domain focuses on lung symptoms and the treatments evaluated in this study are targeted toward the lungs.

QOL-PCD Lower Respiratory Symptoms domain for each QOL-PCD questionnaire version will be analyzed using similar analyses for mixed effect model and waterfall plot as described in Section 8.1 Part A. Note that the mixed effect model will use study baseline for ppFEV1 as a baseline covariate. [redacted]

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

The summary statistics for the actual values and absolute changes from study baseline will be obtained for Lower Respiratory Symptoms domain for [redacted] QOL-PCD questionnaire [redacted].

Part B

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

SGRQ:

SGRQ total score [redacted] will be analyzed using ANCOVA model and waterfall plot as described in Section 8.1 Part B.

The summary statistics for the actual values and absolute changes from study baseline and changes from Part B baseline will be obtained for SGRQ total score [redacted].

QOL-PCD:

QOL-PCD Lower Respiratory Symptoms domain for [redacted] QOL-PCD questionnaire [redacted] will be analyzed using ANCOVA model and waterfall plot as described in Section 8.1 Part B.

The summary statistics for the actual values and absolute changes from study baseline and from Part B baseline will be obtained for Lower Respiratory Symptoms domain for [redacted] QOL-PCD questionnaire [redacted].

[redacted]

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

[redacted]

[redacted]

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

[redacted]

8.5 SUMMARY OF EFFICACY ANALYSES

Table 2 below shows a brief summary of the efficacy analyses aforementioned in Section 8.

Table 2. Summary of efficacy analysis

Part A:

Name	Endpoint	Analyses
Primary efficacy endpoint and analysis	Absolute change in ppFEV1 from **study** baseline at Day 29 within each treatment Period	- Mixed-effects model - Waterfall plot - [redacted] - [redacted]
Secondary efficacy endpoint and analysis - SGRQ	Change in SGRQ total score from **study** baseline, after 28 days of treatment in Part A	For SGRQ total score: - Mixed-effects model - Waterfall plot - Descriptive analysis - [redacted]
Secondary efficacy endpoint and analysis – QOL-PCD	Change in QOL-PCD Lower Respiratory Symptoms domain score from **study** baseline, after 28 days of treatment in Part A	For QOL-PCD Lower Respiratory Symptoms domain: - Mixed-effects model - Waterfall plot - Descriptive analysis - [redacted]

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

[redacted]

Part B:

Name	Endpoint	Analyses
Primary efficacy endpoint and analysis	Absolute change in ppFEV1 from **study** baseline and Part B baseline at Day 29	- ANCOVA model - Waterfall plot - Descriptive analysis
Secondary efficacy endpoint and analysis - SGRQ	Change in SGRQ total score from **study** baseline and **Part B** baseline, after 28 days of treatment in Part B	For SGRQ total score: - ANCOVA model - Waterfall plot - Descriptive analysis

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

Secondary efficacy endpoint and analysis – QOL-PCD	Change in QOL-PCD Lower Respiratory Symptoms domain score from **study** baseline and **Part B** baseline, after 28 days of treatment in Part B	For QOL-PCD Lower Respiratory Symptoms domain: - ANCOVA model - Waterfall plot - Descriptive analysis
[redacted]		

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

10 SAFETY

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. 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 provided by treatment received in Part B. For subjects receiving study drug from more than one treatment group in the same treatment period for Part A, the treatment group allocation will be determined using the following order: VX-371 + HS > VX-371 + Placebo > HS > Placebo.

For safety analysis, the period baselines will be used for Part A and the Part B baseline will be used for Part B. The overall safety profile of study drug will be assessed in terms of the following safety and tolerability endpoints:

- Treatment-emergent adverse event (TEAEs)
- Clinical laboratory values (i.e., urine, serum and plasma chemistry, and hematology)
- ECG results
- Spirometry
- Vital signs
- Pulse oximetry

10.1 ADVERSE EVENTS

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

Pre-treatment AEs are defined as 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.

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

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 B.

For the cases in which the end of treatment emergent Period 2 is on the same day as the start of treatment emergent Period for Part B, any AE starting on the same day as start of treatment emergent Period for Part B, will be assigned to the treatment in Part B.

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

- All TEAEs
- TEAEs by worst/highest relationship (includes Related, Possibly Related, Unlikely Related and Not Related)
- TEAEs by maximum severity (includes Mild, Moderate, Severe, and Life threatening)
- TEAEs leading to treatment discontinuation
- TEAEs leading to drug interruption
- Serious TEAEs
- TEAEs leading to death
- Frequently reported TEAEs

A frequently reported TEAE is defined as more than 2 subjects who have TEAE preferred term incidence for at least 1 treatment group.

Summaries will be presented by treatment and by MedDRA (version 18.1) system organ class (SOC) 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

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

relationship summaries. An AE overview table will be provided for the following categories:

- TEAEs
- Related TEAEs (includes Related and Possibly Related)
- Serious TEAEs
- Related Serious TEAEs
- TEAEs Leading to Study Drug Interruption
- TEAEs Leading to Study Drug Discontinuation
- TEAEs with Outcome of Death

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.

TEAEs related to study device will also be summarized by system organ class and preferred term using frequency counts and percentages (i.e., number and percentage of subjects with an event).

10.2 LABORATORY EVALUATIONS

The actual values and absolute changes from Part A period baseline and Part B baseline for the continuous laboratory parameters will be summarized in SI units by treatment at each scheduled visit for Part A and Part B respectively.

The number and percentage of subjects with at least 1 laboratory abnormality meeting the threshold analysis criteria during the Treatment Emergent Period for Part A and Part B will be summarized by treatment. The Thresholds Range Analyses criteria are provided in Appendix III.

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, potassium and urine sodium to potassium ratios will be summarized by treatment.

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

Serum potassium exceeding 1.1 * upper limit of normal (ULN) and/or plasma potassium exceeding 1.1 * ULN will also be summarized and listed.

10.3 VITAL SIGNS

The actual values and absolute changes from Part A period baseline and Part B baseline for the following vital signs measurements will be presented by treatment at each scheduled visit for Part A and Part B respectively: systolic and diastolic blood pressure (mm Hg), body temperature, pulse rate (beats per minute), respiratory rate (breaths per minute), weight (kg), height (cm) and BMI (kg/m^2). The number and percentage of subjects with at least 1 threshold analysis event during the treatment emergent period will also be tabulated.

The Thresholds Range Analyses criteria are provided in Appendix III.

10.4 ELETROCARDIOGRAM

A summary of actual values and absolute changes from Part A period baseline and Part B baseline will be provided by treatment at each scheduled visit for Part A and Part B respectively for the following electrocardiogram (ECG) measurements: ventricular heart rate, QRS duration, PR duration, QT duration, RR interval, QTcF. In addition, the number and percentage of subjects with at least 1 threshold analysis event during the treatment emergent period will also be tabulated.

The Thresholds Range Analyses criteria are provided in Appendix III.

10.5 PHYSICAL EXAMINATION

For Part A and Part B, abnormal physical examination results will be presented in individual subject data listings only.

10.6 SPIROMETRY

Spirometry data in Part A and Part B will be summarized based on the Part A Safety Set and Part B Safety Set respectively. This will include the number and percentage of subjects at each scheduled time point relative to Part A period baseline value and Part B Baseline value for the following:

- Subjects with ≥10 percentage point decrease in ppFEV1
- Subjects with ≥15 percentage point decrease in ppFEV1
- Subjects with ≥ 20 percentage point decrease in ppFEV1

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

- Subjects with ≥ 0.2 L decrease in FEV1

10.7 PULSE OXIMETRY

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

The number and percentage of subjects with shift changes from Part A period baseline and Part B baseline (normal/missing and low: Normal oxygen saturation: >95%, low oxygen saturation: <=95%) to the lowest percent of oxygen saturation during the Part A and B treatment emergent period will be tabulated by treatment.

10.8 SUMMARY OF SAFETY ANALYSIS

Table 3 below shows a brief summary of the safety analyses aforementioned in Section 10.

Table 3. Summary of safety analysis

Part A:

Name	Analyses
Adverse event	Frequency of TEAEs for different categories
Laboratory	Using Period 1 and Period 2 Baseline: - Descriptive analysis - Threshold range analysis - Descriptive analysis for urine sodium, potassium and urine sodium to potassium ratios
Vital sign	Using Period 1 and Period 2 Baseline: - Descriptive analysis - Threshold analysis
Eletrocardiogram	Using Period 1 and Period 2 Baseline: - Descriptive analysis - Threshold analysis
Spirometry	Using Period 1 and Period 2 Baseline: - Frequency of pre-specified ppFEV1 and FEV1 categories
Pulse Oximetry	Using Period 1 and Period 2 Baseline: - Descriptive analysis - Shift table

Part B:

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

Name	Analyses
Adverse event	Frequency of TEAEs for different categories
Laboratory	Using Part B Baseline: - Descriptive analysis - Threshold range analysis - Descriptive analysis for urine sodium, potassium and urine sodium to potassium ratios
Vital sign	Using Part B Baseline: - Descriptive analysis - Threshold analysis
Eletrocardiogram	Using Part B Baseline: - Descriptive analysis - Threshold analysis
Spirometry	Using Part B Baseline: - Frequency of pre-specified ppFEV1 and FEV1 categories
Pulse Oximetry	Using Part B Baseline: - Descriptive analysis - Shift table

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

11 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Not applicable

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

12 REFERENCE LIST

[1] St George's respiratory questionnaire Manual, June 2009.

[redacted]

[3] Laura Behan, Margaret W Leigh, Sharon D Dell, Audrey Dunn Galvin, Alexandra L Quittner, Jane S Lucas. Validation of a health-related quality of life instrument for primary ciliary dyskinesia (QOL-PCD). Thorax 2017

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

13 PROGRAMMING CONSIDERATIONS

13.1 TABLE, LISTING, AND FIGURE FORMAT

13.1.1 General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 9
- The data displays for all TLFs will have a 1-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.1.2 Headers and Footers

All table and listing headers will be similar in content.

Components of the header and footer include:

- Upper Left, Line 1: "`Parion Sciences Incorporated`"
- Upper Left, Line 2: "`PS-G202 : CLEAN-PCD. Final CSR analysis`"
- Upper Right, Line 1: "`Page X of Y`", where X and Y are the current page number and the total number of pages, respectively

Actual title of the table or listing should start at line 4.

All table and listing footnotes should be consistent:

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Footnotes will be present on the page where they are first referenced and thereafter on each page of the table, unless the footnote is specific only to certain pages. Subject specific footnotes should be avoided.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source:
  - Lower Left, Last Line: "`Program Name: <\\path name>`"
  - Lower Right, Last Line: "`Creation Date and Time: <DDMMMYYYY HH:MM>`"

13.1.3 Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering will be used. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
Safety Set

13.1.4 Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.

13.1.5 Body of the Data Display

13.1.5.1 General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

13.1.5.2 Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- P-values should be output in the format: "0.xxxx", where xxxx is the value rounded to 4 decimal places. Any p-value less than 0.0001 will be presented as <0.0001. If the p-value is returned as >0.9999 then present as >0.9999
- Percentage values should be printed to one decimal places, in parentheses with no spaces, one space after the count (e.g., 7 (12.1%), 13 (5.3%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages equating to 100% should be presented as 100%, without any decimal places.
- For Part A: Tabular display of data for medical history and adverse events should be presented by the body system or SOC with the highest occurrence for VX-371 in 4.2% hypertonic saline group in decreasing order, assuming all terms are coded. Within the body system or SOC, medical history (by preferred term), and adverse events (by preferred term) should be displayed in decreasing order for VX-371 in 4.2% hypertonic saline group. Tabular display of data for prior/concomitant medications should be presented by the ATC level with highest occurrence for VX-371 in 4.2% hypertonic saline group in decreasing order. Within the ATC level prior/concomitant medications (by preferred term) should be displayed in decreasing order for VX-371 in 4.2% hypertonic saline group. If the incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics which cannot be estimated should be reported as "-".
- For Part B: A similar approach will also apply for Part B using the overall column instead of VX-371 in 4.2% hypertonic saline group as the sorting order.
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

should only be output on the first relevant page.

13.1.5.3 Listing Conventions

- Listings will be sorted for presentation in order of treatment groups, subject number, visit/collection day, and visit/collection time.
- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in ISO format ("YYYY-MM-DD": 2000-07-01). If time is collected, the date and time will be presented in format: "YYYY-MM-DDTHH:MM:SS: 2000-07-01T20:13:14". Missing portions of dates should be represented on subject listings as dashes 2000-07--- or 2000-07-01T20:--:--). Dates or date and time that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

13.1.5.4 Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

14 QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analyses. [redacted] provide an overview of the development of such SAS programs.

[redacted] describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output.

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

15 INDEX OF TABLES

For table shells, see ATTACHMENT 1

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

16 INDEX OF LISTINGS

For listing shells, see ATTACHMENT 2

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

17 INDEX OF FIGURES

For figure shells, see ATTACHMENT 3

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

[redacted]

[redacted]

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

[redacted]

[redacted]

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

[redacted]

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

[redacted]

[redacted]

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

[redacted]

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

APPENDIX III LIST OF THRESHOLD RANGE ANALYSIS CRITERIA

Threshold Criteria for **Laboratory Tests**

Parameter	Criteria	Comments
Clinical Chemistry		
CPK	>ULN - ≤ 2.5 x ULN >2.5 - ≤ 5 x ULN >5 - ≤ 10x ULN >10 x ULN	CTCAE grades 1-4
Creatinine	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	CTCAE grades 1-4
Blood Urea Nitrogen	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	Same criteria as creatinine No CTCAE
Sodium	Hyponatremia <LLN - ≥130 mmol/L <130 – ≥120 mmol/L <120 mmol/L	CTCAE grade 1, 3, 4 (No CTCAE grade 2)
	Hypernatremia >ULN - ≤ 150 mmol/L >150 mmol/L- ≤155 mmol/L >155 mmol/L - ≤ 160 mmol/L >160 mmol/L	CTCAE grade 1-4
Potassium (Plasma)	Hypokalemia <LLN – ≥ 2.5 mmol/L <2.5 – ≥ 2.0 mmol/L <2.0 mmol/L	
	Hyperkalemia >ULN – ≤ 5.1 mmol/L	CTCAE grade 1-4

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

	>5.1 – ≤ 5.6 mmol/L >5.6 – ≤ 6.0 mmol/L >6.0 mmol/L	
Potassium (Serum)	Hypokalemia <LLN – ≥ 3.0 mmol/L <3.0 – ≥ 2.5 mmol/L <2.5 mmol/L	CTCAE grade 1&2, 3, 4 (Grade 1 and 2 are the same)
	Hyperkalemia >ULN – ≤ 5.5 mmol/L >5.5 – ≤ 6.0 mmol/L >6.0 – ≤ 7.0 mmol/L >7.0 mmol/L	CTCAE grade 1-4
Glucose	Hypoglycemia <3.0 – ≥ 2.2 mmol/L <2.2 - ≥ 1.7 mmol/L <1.7 mmol/L	CTCAE grade 1-4
	Hyperglycemia >ULN - ≤ 8.9 mmol/L >8.9 – ≤ 13.9 mmol/L >13.9 – ≤ 27.8 mmol/L >27.8 mmol/L	CTCAE grade 1-4
Albumin	<35 - ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4
Lipase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4
Direct bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	Same Criteria as Total Bilirubin No CTCAE Not in DILI Guidance
GGT	>ULN - ≤ 2.5 x ULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	CTCAE grade 1-4
Calcium	Hypercalcemia >ULN - ≤ 2.9 mmol/L >2.9 – ≤ 3.1 mmol/L >3.1 – ≤ 3.4 mmol/L >3.4 mmol/L	CTCAE grade 1-4

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

	Hypocalcemia <LLN - ≥ 2.0 mmol/L <2.0 – ≥1.75 mmol/L <1.75 – ≥ 1.5 mmol/L <1.5 mmol/L	CTCAE grade 1-4
Magnesium	Hypermagnesemia >ULN - ≤ 1.23 mmol/L >1.23 – ≤ 3.30 mmol/L >3.30 mmol/L	CTCAE grade 1, 3, 4 No CTCAE grade 2
	Hypomagnesemia <LLN - ≥ 0.5 mmol/L <0.5 – ≥ 0.4 mmol/L <0.4 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
ALT	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN >5 – ≤ 8 xULN >8 – ≤ 20.0 xULN >20.0 x ULN	Per FDA DILI Guidance Jul 2009 and CTCAE
AST	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN >5 – ≤ 8 xULN >8 – ≤ 20.0 xULN >20.0 x ULN	FDA DILI Guidance and CTCAE
ALT or AST	(ALT>ULN and ALT ≤ 3 xULN) or (AST>ULN and AST≤ 3 xULN) (ALT>3 xULN and ALT ≤ 5 xULN) or (AST>3xULN and AST≤ 5 xULN) (ALT>5 xULN and ALT ≤ 8 xULN) or (AST>5xULN and AST≤ 8 xULN) (ALT>8 xULN and ALT ≤ 20 xULN) or (AST>8xULN and AST≤ 20 xULN) ALT>20 xULN or AST> 20 xULN	FDA DILI Guidance
Alkaline Phosphatase	>ULN - ≤ 1.5xULN >1.5 – ≤ 2.5 xULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	FDA DILI Guidance and CTCAE
Total Bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	FDA DILI Guidance and CTCAE
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	FDA DILI Guidance Jul 2009
Hematology		
WBC	WBC decreased <LLN - ≥ 3.0 x 10e9 /L <3.0 – ≥ 2.0 x 10e9 /L <2.0 – ≥ 1.0 x 10e9 /L <1.0 x 10e9 /L	CTCAE grade 1-4
	Leukocytosis >100 x 10e9 /L	CTCAE grade 3 (only Grade available)
Lymphocytes	Lymphocyte decreased <LLN - ≥ 0.8 x10e9 /L <0.8 – ≥ 0.5 x10e9 /L <0.5 – ≥ 0.2 x10e9 /L <0.2 x10e9 /L	CTCAE grade 1-4
	Lymphocyte increased >4 – ≤ 20 x10e9/L >20 x10e9/L	CTCAE grade 2, 3 (only Grades available)
Neutrophils	Neutrophil decreased <LLN - ≥ 1.5 x10e9 /L <1.5 – ≥ 1.0 x10e9 /L <1.0 – ≥ 0.5 x10e9 /L <0.5 x10e9 /L	CTCAE grade 1-4
Hemoglobin	Hgb decreased (anemia) <LLN - ≥ 100 g/L <100 – ≥ 80 g/L < 80 g/L	CTCAE grade 1-3
	Hgb increased >ULN - ≤ 20 g/L above ULN >20 g/L above ULN - ≤ 40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3
Platelets	Platelet decreased <LLN - ≥ 75.0 x 10e9 /L <75.0 – ≥ 50.0 x 10e9 /L <50.0 – ≥ 25.0 x 10e9 /L <25.0 x 10e9 /L	CTCAE grade 1-4

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

Threshold Criteria for ECGs

Parameter	Criteria	Comments
HR	Bradycardia	Per HV grade 2, 3, plus shift change
	<50 bpm	
	<45 bpm	
	Decrease from baseline ≥10 bpm	
	Decrease from baseline ≥20 bpm	
	<50 bpm and decrease from baseline ≥10 bpm	
	<50 bpm and decrease from baseline ≥20 bpm	
	Tachycardia	Per HV grade 1, 2, 3, plus shift change
	>100 bpm	
	>115 bpm	
	>130 bpm	
	Increase from baseline ≥10 bpm	
	Increase from baseline ≥20 bpm	
	>100 bpm and increase from baseline ≥10 bpm	
	>100 bpm and increase from baseline ≥20 bpm	
PR	≥240 ms	
	≥300 ms	
	≥200 ms and increase from baseline ≥40 ms	
	≥200 ms and increase from baseline ≥100 ms	
QRS	>110 ms	
	>160 ms	
	Increase from baseline ≥20 ms	
	Increase from baseline ≥40 ms	
QTcF	>450 ms (Male)	
	>470 ms (Female)	
	≥500 ms	
	Increase from baseline >10 ms	
	Increase from baseline >20 ms	
	Increase from baseline >40 ms	
	Increase from baseline >60 ms	

Threshold Criteria for Vital Signs

Parameter	Threshold Criteria	Comments
HR	Same PCS as above in ECG category	

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

SBP	SBP increased	809/770 analyses
	>140 mmHg	
	>160 mmHg	
	>10 mmHg increase from baseline	
	>20 mmHg increase from baseline	
	>140 mmHg & >10 mmHg increase from baseline	
	>140 mmHg & >20 mmHg increase from baseline	
	>160 mmHg & >10 mmHg increase from baseline	
	>160 mmHg & >20 mmHg increase from baseline	
	SBP decrease	Per HV grade 1, 3, plus shift change
	<90 mmHg	
	<80 mmHg	
	>10 mmHg decrease from baseline	
	>20 mmHg decrease from baseline	
	<90 mmHg and >10 mmHg decrease from baseline	
	<90 mmHg and >20 mmHg decrease from baseline	
	<80 mmHg and >10 mmHg decrease from baseline	
	<80 mmHg and >20 mmHg decrease from baseline	
DBP	DBP increased	809/770 analyses
	>90 mmHg	
	>100 mmHg	
	>5 mmHg increase from baseline	
	>10 mmHg increase from baseline	
	>90 mmHg and >5 mmHg increase from baseline	
	>90 mmHg and >10 mmHg increase from baseline	
	>100 mmHg and >5 mmHg increase from baseline	
	>100 mmHg and >10 mmHg increase from baseline	

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

	DBP decreased	
	<60 mmHg	
	<45 mmHg	
	>5 mmHg decrease from baseline	
	>10 mmHg decrease from baseline	
	<60 mmHg and >5 mmHg decrease from baseline	
	<60 mmHg and >10 mmHg decrease from baseline	
	<45 mmHg and >5 mmHg decrease from baseline	
	<45 mmHg and >10 mmHg decrease from baseline	
Weight	Weight gain	CTCAE grade 1-3
	≥5 % increase from baseline	
	≥10 % increase from baseline	
	≥ 20% increase from baseline	
	Weight loss	CTCAE grade 1-3
	≥5 % decrease from baseline	
	≥10 % decrease from baseline	
	≥ 20% decrease from baseline	

1006696
Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

APPENDIX IV SCHEDULES OF ASSESSMENTS

Table 5. 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.

1006696
Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

Table 6. 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.

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

Statistical Analysis Plan

	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.

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

Statistical Analysis Plan

	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.

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

Statistical Analysis Plan

	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]

1006696
Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

Table 7. 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]		
Spirometry	X	
Urine pregnancy test	X	
Hematology	X	
Urine tests[h]	X	
Serum chemistry	X	
Plasma chemistry[i]	X	
[redacted]		
Collect unused study drug and perform study drug count	X	
Collect subject diary	X	
[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]
expectorated prior to spirometry, if possible.

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

[i] Plasma potassium.

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

Statistical Analysis Plan

APPENDIX V HANDLING MISSING DATE

Prior/Concomitant medication:

Missing or partial medication start date:

- If only day is missing, use the first day of the month.
- If day and month are both missing, use the first day of the year.
- If day, month and year are all missing, use a date before the first dose date (in practice, use Jan. 01, 2000 to impute).

Missing or partial medication stop date:

- If only day is missing, use the last day of the month.
- If day and month are both missing, use the last day of the year.
- If day, month and year are all missing, assign 'continuing' status to stop date (in practice, use Dec. 31, 2050 to impute).

Adverse Event:

Imputation of missing AE start date:

- If AE start date is completely missing and AE end date is after the first dose date in Part A Period 1 but before first dose date in Part B, then use the first dose date in Part A Period 1 as the AE start date and classify the AE as a TEAE; if the AE end date is after the first dose date in Part B then

  1) Use the first dose date in Part A Period 1 as the AE start date

  2) Use the first dose date in Part B as the AE start date.

- If AE start date is completely missing, and AE end date is before the first dose date in Part A Period 1, then the AE is not a TEAE.

- If both AE start date and AE end date are completely missing then

  1) Use the first dose date as AE start date in Part A Period 1 and classify the AE as a TEAE for Part A

  2) Use the first dose date as AE start date in Part B and classify the AE as a TEAE for Part B

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

Statistical Analysis Plan

- If only day is missing, use the first day of the month or the first dose date whichever is later, unless the AE start month is before the first dose date in which case, the AE start date remains missing and this AE is not a TEAE.

- If day and month are both missing, use the first day of the year or the first dose date whichever is later, unless the AE start year is before the first dose date. In this case, the AE start date remains missing and this AE is not a TEAE.

Imputed AE start date must be earlier than the original AE end date, otherwise set imputed start date = original AE end date and the AE is not a TEAE.

Missing AE causality

For summary tables of related AEs, report missing causality as 'related'.

Missing AE Severity

There will be no imputation of missing AE severity.

Missing SAE category

There will be no imputation of missing SAE category.

1006696
Parion Sciences Incorporated
CLEAN-PCD
SAP Version 1.0

[redacted]

Statistical Analysis Plan

APPENDIX VI VISIT WINDOWS

The unscheduled or early withdrawal visit will be mapped to a scheduled visit for analysis using the date of collection/assessment as a basis to determine study day and then study day will be mapped to the intended visit. Table 8 and Table 9 below contain the analysis visit windows.

Table 8. Study windows

Study Period	Scheduled Visit/Day	Study Day Window	Analysis Visit
Period 1	Day 15 Visit	Day >1 – ≤ 22	Day 15
	Day 29 Visit	Day >22 – ≤ 36	Day 29
Period 2	Day 71 Visit	Period 2, Day >1 – ≤ 22	Day 15
	Day 85 Visit	Period 2, Day >22 – ≤ 36[a]	Day 29
Period 3	Day 99 Visit	Period 3, Day >1 – ≤ 22	Day 15
	Day 113 Visit	Period 3, Day >22 - ≤ 36	Day 29

a: all assessments should happen before Part B dosing time.

For SGRQ, QOL-PCD [redacted] hematology, height and weight, [redacted] the following windows will be used:

Table 9. Study windows for Day 1 and Day 29 only

Study Period	Scheduled Visit/Day	Study Day Window	Analysis Visit
Period 1	Day 29 Visit	Day >1 – ≤ 36	Day 29
Period 2	Day 85 Visit	Period 2, Day >1 – ≤ 36[a]	Day 29
Period 3[b]	Day 113 Visit	Period 3, Day >1	Day 29

a: all assessments should happen before Part B dosing time.
b: visit windows for height and weight will only be applied for Period 1 and 2. Height and weight visit windows for Period 3 will be the same as table 6.

Once analysis visit windows are assigned, all visits, including scheduled visits, unscheduled visits, and early termination visits will be eligible for being flagged as the "analyzed record" within the analysis visit window. Note that the scheduled visit should match with the visit for which the visit window is defined. For example: If Day 29 visit falls in the visit window for Day 15, then Day 15 will be assigned to this visit. If no numerical measurement is available within a visit window, the measurement will be considered missing for the visit.

A subject's individual analysis visit window could potentially contain more than one visit. In the event of multiple visits falling within an analysis visit window or in case of a

1006696

Parion Sciences Incorporated

CLEAN-PCD

SAP Version 1.0

[redacted]

Statistical Analysis Plan

tie, the following rules will be used in sequence to determine the “analyzed record” for the analysis visit window:

- the data closest to the scheduled day will be used.
- If there are multiple measurements with the same distance from the target day, the latest measurement will be used.

The data not flagged as the “analyzed record” will only be listed in subject listings.