VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan

Methods

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

Vertex Study Number: VX15-770-123

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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Term
ALT	alanine transaminase
ALP	alkaline phosphatase
AST	aspartate transaminase
BMI	body mass index (kg/m2)
bpm	beats per minute
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator gene
CRO	contract research organization
CSP	clinical study protocol
[redacted]	
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
$FEF_{25-75\%}$	forced midexpiratory flow rate (L/sec)
FEV_1	forced expiratory volume (L) in 1 second
FVC	forced vital capacity (L)
GGT	gamma-glutamyltranspeptidase
IV	intravenous
IWRS	Interactive Web Response System
LCI	Lung Clearance Index
LFT	liver function test
MBW	Multiple breath Washout
PD	pharmacodynamic/pharmacodynamics
PK	pharmacokinetic/pharmacokinetics
q12h	every 12 hours
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SFU	safety follow-up
SI	système international
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

3. SUMMARY OF MODIFICATIONS

3.1 Modifications from the Approved Clinical Study Protocol

There are no modifications from the approved Clinical Study Protocol (CSP) (Version 4.0, 12 April 2017).

3.2 Modifications from the Approved Statistical Analysis Plan

This is the first version of the Statistical Analysis Plan (SAP) for the final analysis of the study.

4. INTRODUCTION

This final Analysis Plan is based on the information contained in the CSP VX15-770-123 Version 4.0, dated 12 April 2017.

Vertex Biometrics department or a designated contract research organization (CRO) will perform the statistical analysis of the efficacy and safety data; SAS version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the clinical database lock.

Following review of study enrollment and assessment of the available number of potential subjects for this study, Vertex decided to close enrollment as of 21 February 2017 and withdraw subjects in order to terminate the study. After the protocol amendment has been approved at a site, subjects in Part 1 will be withdrawn from the study at their Week 24 Visit, and subjects in Part 2 will be withdrawn from the study and requested to complete the Early Termination of Treatment Visit. The SAP text will use original text from the protocol for objectives and study design, however, the final analysis will be based mainly on Part 1 data due to the small amount of data available for Part 2.

5. STUDY OBJECTIVES

5.1 Primary Objective

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

5.2 Secondary Objectives

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

[redacted]

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

6. STUDY ENDPOINTS

6.1 Part 1

6.1.1 Primary Endpoint

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

6.1.2 Secondary Endpoints

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

[redacted]

7. STUDY DESIGN

7.1 Overview of Study Design

This is a 2- part, randomized, double- blind, placebo- controlled, crossover study with a long-term open- label period. A schematic figure of the study design is presented in Appendix A.

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

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

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

This study includes:

- Screening Period: Day -28 through Day -1 relative to the first dose of study drug
- Part 1 Treatment Period 1 through Treatment Period 2

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

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

Subjects will continue to complete all other scheduled study visits for assessments of efficacy and other endpoints as detailed in the Schedule of Assessments. Subjects who discontinue study drug treatment during Part 1 will not be allowed to participate in Part 2 of the study.

7.2 Sample Size and Power

It is planned that up to a maximum of approximately 50 subjects will be enrolled in this study. As shown in Table 7.1, a sample size of 50 subjects will provide approximately 80% power to detect a treatment difference in mean change from study baseline in LCI (difference between ivacaftor and placebo in the change from study baseline) of 1.5 points. The calculation is based on a paired t-test with a 2-sided significance level of 0.05, and assumes that the within-subject standard deviation (SD) for the difference in change from study baseline for the 2 periods is 3.5 points, and that the dropout rate is about 10% for Part 1.

Different scenarios are presented in Table 7 .1 for the variability and the magnitude of the treatment effect based on 80% power and 2-sided significance level of 0.05. The most conservative scenarios are presented in the last 2 rows of the table (i.e., treatment effect of 1.0 and 1.5, respectively).

Table 7-.1 Sample Size Calculation Corresponding to Different Values of Treatment Effect on Lung Clearance Index Change-From-Predose

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

Table 7-.1 Sample Size Calculation Corresponding to Different Values of Treatment Effect on Lung Clearance Index Change-From-Predose

Treatment Effect (points) on LCI Change From Study Baseline	Standard Deviation of Paired Treatment Difference in LCI Change From Study Baseline	N
1.5	3.5	50

7.3 Randomization

In Part 1, subjects will be randomized in a 1:1 ratio to:

Treatment Sequence 1 (ivacaftor → washout → placebo) or
Treatment Sequence 2 (placebo → washout → ivacaftor).

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

7.3.1 Blinding

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

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

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations
- Unblinded statistician preparing the final (production) randomization list who is not part of the study team
- Vendor preparing the unblinded analysis for the IDMC
- Vertex Data Management IWRS management
- Vertex Clinical Supply Chain

<u>LCI Data Blinding</u>

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

8. ANALYSIS SETS

8.1 Full Analysis Set

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

8.2 Safety Set

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

9. STATISTICAL ANALYSIS

9.1 General Considerations

The study assessments and time points schedule is provided in Appendix B.

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

Categorical variables will be summarized using counts and percentages.

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

For Part 1: The study baseline is defined as the most recent non-missing measurement collected prior to the initial administration of study drug in Treatment Period 1. Period baseline is defined as the most recent non-missing measurement collected before the initial administration of study drug in each Treatment Period. For Treatment Period 1, the period baseline will be the study baseline; for Treatment Period 2, the period baseline will be from an assessment measured after the Washout Period.

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

For Treatment Sequence 1 (ivacaftor->washout->placebo), period baseline will be defined as the most recent non-missing measurement collected prior to initial administration of ivacaftor in the Open-label Period (Part 2).

For Treatment Sequence 2 (placebo->washout->ivacaftor), period baseline will be the same as period baseline for Treatment Period 2 in Part 1 (i.e., the Week 16 Visit).

Efficacy analyses will be based on change from study baseline. However, efficacy analyses based on change from period baseline will also be presented. Similarly, summary tables, as applicable, will be presented based on both baselines.

Treatment Emergent (TE) Period:

- For Treatment Period 1 of Part 1, the TE period will be from the first dose of study drug in Treatment Period 1 of Part 1 to the earliest of the following:
    1) 28 days after the date of subject's treatment completion during Treatment Period 1
    2) Safety Follow-up Visit if discontinued study early during Treatment Period 1
    3) 28 days after the last dose of the study drug for subjects who discontinued the study early during Treatment Period 1 and do not have a Safety Follow-up Visit
- For Treatment Period 2 of Part 1, the TE period will be from the first dose of study drug in the Treatment Period 2 of Part 1 to the earliest of the following:
    1) The date of treatment completion of Treatment Period 2
    2) Safety Follow-up Visit if discontinued study early during Treatment Period 2
    3) 28 days after the last dose of the study drug for subjects who discontinued the study early during Treatment Period 1 and do not have a Safety Follow-up Visit
- For Part 2, the TE period will be from the first dose of study drug in Part 2 to the earliest of the following:
    1) The Safety Follow-up Visit,
    2) 28 days after the last dose of the study drug for subjects who discontinued the study during Part 2 and do not have a Safety Follow-up Visit,

Visit Windowing Rules: Appendix C defines the windows for protocol-defined visits. The windows will be applied using the following rules for both scheduled and unscheduled visits. If no measurement is available within a visit window, the assessment will be considered missing for the visit. If there is more than one measurement available within the same visit window, the following rules will be used:

- For all safety parameters, if there are multiple measurements within a visit window, then 1) the record closest to the target day will be used, with the exception of the threshold analysis in which the worst record will be used; 2) if there are multiple records within the same distance of the target day, the latest record will be used; or 3) the Safety Follow-Up (SFU) visit will not be windowed; instead, the nominal visit will be used in relevant analyses.
- For all efficacy parameters, if there are multiple measurements within a visit window, the record at the scheduled visit will be used. Otherwise,
    - If there are no measurements at the scheduled visit, then the record closest to the target day will be used;
    - If there are multiple records with the same distance to the target day, the latest record will be used.
    - Assessments at the early treatment termination (ETT) visit will follow the windowing rules for regular visits.
    - Assessments at safety follow-up (SFU) visit will follow the windowing rules for regular visits if they fall within the upper boundary of the window for the last scheduled visit; it will remain as the SFU if it goes beyond the upper boundary of the window for the last scheduled visit.

Incomplete/Missing data: Missing data (e.g., dates) will remain as missing in the listings, and conservative conventions established will be used to derive specified parameters for summaries.

Outliers: No formal statistical analyses will be performed to detect and/or remedy the presence of statistical outliers.

Data Presentation:

Where applicable and possible, data will be presented by ivacaftor dose group (50mg, 75mg and 150mg), placebo and overall ivacaftor dose group. For summary statistics, descriptive statistics will be presented for each visit and change from period baseline.

Unscheduled Visits: Unscheduled visit measurements will be included in the following:

- derivations of measurements at scheduled visits per specified visit windowing rules;
- derivations of baseline/last on-treatment measurements;
- derivations of the maximum/minimum on-treatment values and maximum/minimum changes from baseline values for safety analyses;
- data listings where appropriate.

9.2 Background Characteristics

9.2.1 Subject Disposition

The subject disposition will be summarized in both a table and a listing. The number of subjects in the following categories will be presented:

- Randomized
- FAS
- Safety Set

The number and percentage (based on Safety Set) of subjects in each of the following disposition categories will be presented:

- Completed study drug treatment regimen of Part 1 Treatment Period 1
- Prematurely discontinued the treatment and the reason for discontinuations during Part 1 Treatment Period 1
- Completed study drug treatment regimen of Part 1 Treatment Period 2
- Prematurely discontinued the treatment and the reason for discontinuations during Part 1 Treatment Period 2
- Continue into Part 2
- Prematurely discontinued the study and the reasons for discontinuations

9.2.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics data will be summarized in both a table and a listing based on Safety Set by treatment sequence.

Demographic data will include the following:

- Sex (female and male)
- Age
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other)
- Geographic region (by each country)

Baseline characteristics will include the following:

- Weight (kg)

[redacted]

- Height (cm)

[redacted]

- BMI (kg/m^2)

[redacted]

The following disease characteristics will be listed only:

- *CFTR* mutation at screening
- Ophthalmologic examinations at screening

9.2.3 Medical History

Medical history in this study will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA).

Medical history data will be summarized descriptively by system organ class and preferred term based on Safety Set by the treatment group. The corresponding data listing will also be provided.

9.2.4 Prior and Concomitant Medications

Medications used in this study will be coded by using the World Health Organization Drug Dictionary Enhanced (WHODDE) and categorized as the following:

- **Prior medication:** any medication that started before the first dose of study drug, regardless of when it ended.
- **Concomitant medication:** medication continued or newly received during the TE period for Treatment Period 1 or Treatment Period 2. If a subject took a medication during a specific Treatment Period, this medication will be attributed to the study drug the subject received

during this Treatment Period. As a result, 1 medication could be attributed to more than 1 study drug for an individual subject.

- **Post-treatment medication:** medication continued or newly received beyond the TE period for Treatment Period 2, or between the TE periods for Treatment Period 1 and Treatment Period 2, or beyond the TE period for Treatment Period 1 for subjects who do not have Treatment Period 2.

Prior medications and concomitant medications will be listed only.

9.2.5 Study Drug Exposure

Exposure summaries will be based on the Safety Set.

Duration of study drug exposure is defined as: last dose date – first dose date + 1 day, regardless of any interruption in dosing between the first and the last dose for each treatment period. The duration will be calculated for the treatment corresponding to each treatment period.

Total exposure (in patient years) and duration of study drug exposure will be summarized descriptively (number, mean, SD, SE, median, minimum, and maximum). Total exposure is defined as the sum of the subject's duration of treatment exposure and expressed in patient years. Duration of exposure will also be summarized into categories as the following: ≥1 day, ≥1 week, ≥2 weeks, ≥4 weeks, ≥8 weeks.

9.2.6 Study Drug Compliance

Study drug compliance based on the number of tablets/sachets taken will be calculated as: 100 × [(total number of study drug dispensed) – (total number of study drug returned)]/ (total number of study drug planned to be taken per day × duration of study drug exposure in days). The maximum percentage of study drug taken will be 100%.

Study drug compliance based on study drug exposure will be calculated as: 100 × [1 − (total number of days of any study drug interruption) / (duration of study drug exposure in days)].

Study drug compliance will be summarized descriptively by the number of subjects (n), mean, SD, SE, median, min, and max.

Study drug compliance summaries will be based on the Safety Set.

9.2.7 Important Protocol Deviations / Violations

An important protocol deviation and violation is a protocol deviation or violation that has the potential to affect the interpretation of study results. PD/PV will be identified from the clinical database and/or site deviation log.

The rules for identifying PD/PVs will be included in an internal Biometrics document.

All PD/PV will be presented as an individual subject data listing only.

9.3 Efficacy Analysis

9.3.1 Analysis of the Primary Efficacy Variable

The primary efficacy variable is the absolute change from baseline through 8 weeks of treatment in LCI endpoint.

LCI will be summarized using descriptive statistics and will also be presented for each visit and change from period baseline.

Due to the low sample size of the study the planned MMRM analyses will not be carried out as the mixed effect model is likely to be unstable.

Because of the low expected power, a Bayesian analysis will be performed. A Bayesian analysis on within-subject treatment difference, i.e. difference between the averages of the week 4 and week 8 LCI measurements on ivacaftor and placebo. The Bayesian approach calculates the posterior probability that the treatment difference is less than zero, which can be obtained from a frequentist one sample t-test. There are no specific success criteria due to the low subject numbers available for analysis

9.3.2 Analysis of the Secondary Efficacy Variables

Absolute change from period baseline in serum levels of immunoreactive trypsinogen at 8 weeks of treatment will be summarized using summary statistics only. In addition a data listing of IRT data will be produced. As two different IRT assays were used these data will be analyzed in two separate subsets classified by their assay platforms and analyzed by period baseline.

Absolute change from baseline in fecal elastase-1 at 8 weeks of treatment will be summarized using summary statistics only. In addition a data listing will be produced.

Absolute change from baseline in weight at 8 weeks of treatment will be summarized using summary statistics only. In addition a data listing will be produced.

Absolute change from baseline in body mass index (BMI) at 8 weeks of treatment will be summarized using summary statistics only. In addition a data listing will be produced.

[redacted]

9.4 Safety Analysis

The safety profile of study drug will be assessed in terms of the following safety and tolerability data from Part 1:

- Adverse events
- Clinical laboratory values (hematology, serum chemistry, liver function tests, coagulation studies, and urinalysis)
- Vital signs
- Ophthalmology

Safety endpoints will be analyzed based on the Safety Set (for each applicable treatment period). Only descriptive analysis of safety will be performed and no statistical testing will be performed.

9.4.1 Adverse Events

For analysis purposes, adverse events will be classified as pre-treatment emergent, TEAE, or post-treatment emergent. Adverse events which start (or increase in severity) during the period from the signing of informed consent up to, but not including, the first dose of study drug will be considered pre-treatment. Adverse events which start (or increase in severity) during the period from the first dose of study drug through completion of the Follow-up Visit will be considered TEAE. Adverse events which start (or increase in severity) after the completion of the Follow-up Visit will be considered post-treatment adverse events.

If an adverse event started (or increased in severity) during a specific treatment period, this adverse event will be attributed to the study drug the subject is receiving during this Treatment Period. Adverse events that started (or increased in severity) during the Washout Period and within 28 days of the last dose of treatment period 1 will be attributed to the treatment received in Treatment Period 1. Please see Section 9.1 for details.

For determining whether the AEs with missing or partially missing dates are treatment-emergent, please refer to Appendix D for rules. Please note that no imputation will be displayed in the listing outputs.

Adverse event summary tables will be presented for TEAE only and will include the following:

All TEAEs,

Related (defined as possibly related or related) TEAEs,

TEAEs leading to treatment discontinuation,

Serious TEAEs,

TEAEs by severity,

TEAEs by relationship.

Summaries will be presented by MedDRA system organ class and preferred term using frequency counts and percentages (i.e., number and percentage of subjects with an event). Subjects with multiple occurrences of the same adverse event or a continuing adverse event will be counted once, and only the maximum severity level will be presented in the severity summaries, and the worst/highest relationship level in the relationship summaries. In addition,

listing containing individual subject adverse event data for all deaths and other serious and significant adverse events will be provided, separately. All adverse events including Pre- and Post-treatment adverse events will be presented in individual subject data listings.

Imputation rules for missing or partial AE dates are presented in Appendix D.

9.4.2 Clinical Laboratory

The following analyses for the lab assessments will be presented:

- Post-baseline values and change from baseline for chemistry, hematology, and LFT results will be summarized using SI units by treatment group at each scheduled time point.
- Abnormal hematology, chemistry, and LFT results will be summarized at each visit and also listed. Both abnormal low and high will be presented for hematology and chemistry results. Only abnormal high (elevated LFT) will be presented for LFT results.
- Number and percentage of subjects with abnormal LFT results meeting the threshold criteria will be summarized by treatment group at each scheduled time point. The threshold criteria for abnormal are provided in Appendix E. Results will also be presented overall by treatment group.
- The shift incidence of LFT results meeting threshold criteria against the baseline threshold criteria will be summarized by treatment group at each scheduled time point (only shifts to values worse than baseline will be presented).
- Box plots for the Ratio of LFT results to the ULN will be plotted against visit for each treatment group.
- Mean values (±SD) will be plotted against visit for ALT, AST, ALP, total bilirubin, and GGT for each treatment group.
- A scatterplot based on multiples of ULN will be provided for peak ALT versus peak total bilirubin and peak AST versus peak total bilirubin during the TE Period for each treatment group.
- Results of urinalysis and coagulation studies (only collected at screening) will be listed in individual subject data listings.

LFT includes ALT, AST, ALP, total bilirubin, and GGT. When presenting data for ALT and AST and additional category for ALT/AST (ALT or AST) will be presented.

Threshold analysis criteria for LFTs are presented in Appendix E.

9.4.3 Vital Signs

The vital signs data will be presented in a listing: systolic and diastolic blood pressure (mm Hg), body temperature (^{o}C), HR (beats per minute), and respiratory rate (breaths per minute).

9.4.4 Ophthalmologic Examination

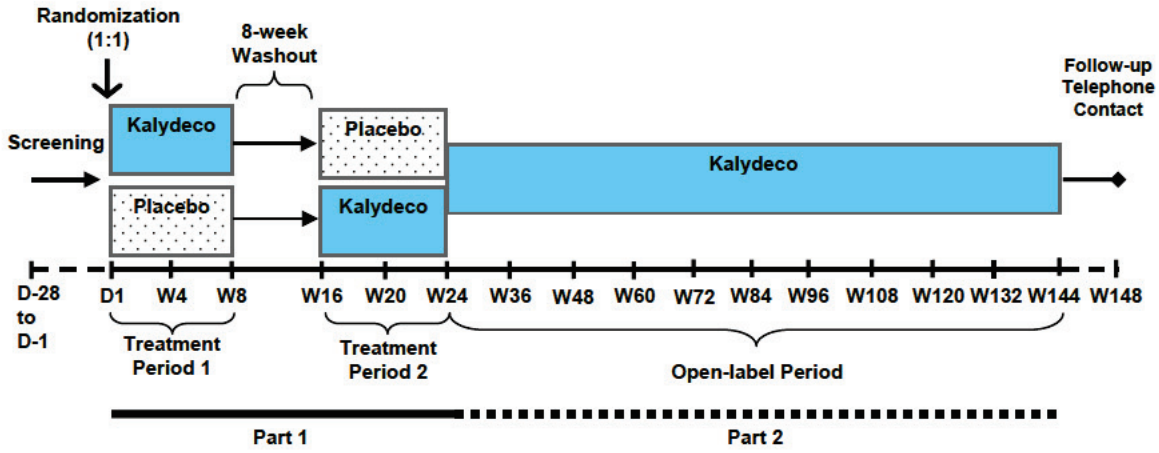
The ophthalmologic examination data will be presented in a listing.

9.4.5 Physical Examination

Physical examination data will be presented in a listing.

10. LIST OF APPENDICES

Appendix A: Schematic of Study Design



Appendix B: Schedule of Assessments

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

Event/Assessment	Screening Period (Day -28 to Day -1)[1]
Clinic visit	X
Informed consent/assent	X
Inclusion/exclusion criteria review	X
Demography	X
CFTR genotype[2]	X
Medical history	X
Prior and concomitant medications	X
Height and weight	X
Physical examination and vital signs[3]	X
Multiple breath washout[4]	X
Coagulation	X
Serum chemistry	X
Hematology	X
Urinalysis	X
Ophthalmologic examinations[5]	X
Immunoreactive trypsinogen[6]	X
Fecal sample collection[7]	X
Adverse events	Continuous from signing of ICF through end of study participation

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

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

[3] See Section 11.5.3.

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

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

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

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

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

	Part 1 Placebo-controlled Crossover Period[8]							Part 2 Open-label Period[8] (Wk 24 to Wk 144)								
	Treatment Period 1 (Day 1 to Wk 8)			Wash-out	Treatment Period 2 (Wk 16 to Wk 24)											
Event/ Assessment	**Day 1**	**Wk 4 (± 3 days)**	**Wk 8 (± 5 days)**	**8 Wks (± 5 days)**	**Wk 16 (± 3 days)**	**Wk 20 (± 3 days)**	**Wk 24 (± 5 days)**	**Wk 36 (± 2 wks)**	**Wk 48 (± 2 wks)**	**Wk 60 (± 2 wks)**	**Wk 72 (± 2 wks)**	**Wk 84 (± 2 wks)**	**Wk 96 (± 2 wks)**	**Wk 108 (± 2 wks)**	**Wk 120 (± 2 wks)**	**Wk 132 (± 2 wks)**	**Wk 144 (± 2 wks)**
Clinic visit	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria review	X																
Randomization[9]	X																
Concomitant medications	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant treatments and procedures	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Height and weight	X		X		X		X	X	X	X	X	X	X	X	X	X	X

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

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

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

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

	Part 1 Placebo-controlled Crossover Period[8]								Part 2 Open-label Period[8] (Wk 24 to Wk 144)								
	Treatment Period 1 (Day 1 to Wk 8)			Wash-out	Treatment Period 2 (Wk 16 to Wk 24)												
Event/ Assessment	**Day 1**	**Wk 4 (± 3 days)**	**Wk 8 (± 5 days)**	**8 Wks (± 5 days)**	**Wk 16 (± 3 days)**	**Wk 20 (± 3 days)**	**Wk 24 (± 5 days)**	**Wk 36 (± 2 wks)**	**Wk 48 (± 2 wks)**	**Wk 60 (± 2 wks)**	**Wk 72 (± 2 wks)**	**Wk 84 (± 2 wks)**	**Wk 96 (± 2 wks)**	**Wk 108 (± 2 wks)**	**Wk 120 (± 2 wks)**	**Wk 132 (± 2 wks)**	**Wk 144 (± 2 wks)**
Multiple breath washout[10]	X	X	X		X	X	X		X				X				X
[redacted]																	
Serum chemistry[12]	X		X		X		X	X	X		X		X				X
Hematology	X		X		X		X	X	X		X		X				X
Ophthalmologic examinations									X				X				X
Immunoreactive trypsinogen[13]	X		X		X		X		X				X				X
Fecal sample collection[14]			X		X		X		X				X				X

[10] At least 3 MBW tests will be performed (see Section 11.4.1 and the Study Reference Manual). The assessment will be performed before the spirometry [redacted]

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

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

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

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

	Part 1 Placebo-controlled Crossover Period[8]							Part 2 Open-label Period[8] (Wk 24 to Wk 144)								
	Treatment Period 1 (Day 1 to Wk 8)			Wash-out	Treatment Period 2 (Wk 16 to Wk 24)											
Event/ Assessment	**Day 1**	**Wk 4 (± 3 days)**	**Wk 8 (± 5 days)**	**8 Wks (± 5 days)**	**Wk 16 (± 3 days)**	**Wk 20 (± 3 days)**	**Wk 24 (± 5 days)**	**Wk 36 (± 2 wks)**	**Wk 48 (± 2 wks)**	**Wk 60 (± 2 wks)**	**Wk 72 (± 2 wks)**	**Wk 84 (± 2 wks)**	**Wk 96 (± 2 wks)**	**Wk 108 (± 2 wks)**	**Wk 120 (± 2 wks)**	**Wk 132 (± 2 wks)**	**Wk 144 (± 2 wks)**
[redacted]																	
Meal or snack at study center[16]	X	X	X		X	X	X		X				X				X
Study drug dosing at study visit[16]	X	X	X[17]		X	X	X[18]		X				X				X
Dispense study drug[19]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	
Study drug count	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																	
Adverse events	Continuous from signing of ICF through end of study participation																
[redacted]																	

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

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

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

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

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

Event/Assessment	Early Termination of Treatment Visit[20]	Safety Follow-up Visit 4 weeks (±7 days) After Last Dose of Study Drug[20]	Follow-up Telephone Contact 4 weeks (±7 days) After the Week 144 Visit
Clinic visit	X	X	
Telephone Contact			X
Concomitant medications	X	X	
Concomitant treatments and procedures	X	X	
Height and weight	X	X	
Serum chemistry	X	X	
Hematology	X	X	
Ophthalmologic examinations[21]	X		
[redacted]			
Study drug count	X		
[redacted]			
Adverse events	Continuous from signing of ICF through end of study participation		

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

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

[redacted]

Appendix C: Visit Window Mapping Rules for Efficacy and Safety Measurements

Table 10-4 Visit Window Mapping Rules (within Period)

Assessments	Period - Visit	Analysis Visit	Target Study Day	Visit Window (in study days)
• Labs o Chemistry o Hematology o Liver Function Tests o Weight, Height.	1 - Day 1	Day 1	1	[1, 1]
	1 - Week 8	Week 8	57	[2, 85]
	2 - Week 16	Day 1	1	[1, 1]
	2 - Week 24	Week 8	57	[2, Date of Week 24 visit]
	2 – Safety Follow-up Visit	Safety Follow-up Visit	NA	Use the nominal visit name
• LCI	1 - Day 1	Day 1	1	[1, 1]
	1 - Week 4	Week 4	28	[2, 42]
	1 - Week 8	Week 8	57	[43, 85]
	2 - Week 16	Day 1	1	[1, 1]
	2 - Week 20	Week 4	28	[2, 42]
	2 - Week 24	Week 8	57	[43, Date of Week 24 visit]
	2 – Safety Follow-up Visit	Safety Follow-up Visit	NA	Use the nominal visit name

Appendix D: Imputation Rules for Missing or Partial AE Dates

For missing or partial AE start date, use the imputation rules below for the purpose of determining whether an AE is treatment-emergent. The imputed dates will not be displayed in the listing outputs.

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date; otherwise, impute the AE start day as 1.
- Otherwise, impute the AE start day as 1.

Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date; otherwise, impute the AE start Month as January and the Day as 1.
- Otherwise, impute the AE start MONTH as January and the DAY as 1.

Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site with no imputation. Also compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date then the AE should be considered as a pretreatment AE. Otherwise, the AE will be considered as TEAE.

Missing or partially missing AE end date will not be imputed.

Appendix E: Threshold Analysis Criteria

Table 11-5 CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT EVENT

Parameter	Threshold 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	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
Total Cholesterol	>ULN – ≤ 7.75 mmol/L >7.75 – ≤ 10.34 mmol/L >10.34 – ≤ 12.92 mmol/L >12.92 mmol/L	CTCAE grade 1-4
Triglycerides	>1.71 – ≤ 3.42 mmol/L >3.42 – ≤ 5.7 mmol/L >5.7 – ≤ 11.4 mmol/L >11.4 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
	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
Inorganic phosphate	Hypophosphatemia <0.74 – ≥ 0.6mmol/L <0.6 – ≥ 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>3xULN or AST>3xULN	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
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

Note: Sources utilized for threshold analyses:
- NCI CTC-AE v4.03;
- FDA Guidance for Industry – DILI: Premarketing Clinical Evaluation.
- FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical trials;

[i] Centers for Disease Control and Prevention. CDC Growth Charts. Available at: http://www.cdc.gov/growthcharts/percentile_data_files.htm. Accessed 16 May 2012.