VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX16-770-127 Version 1.0

A Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy of Ivacaftor in Subjects with Cystic Fibrosis Who are 6 Years of Age and Older and Have Either a 3849 + 10KB C→T or D1152H-CFTR Mutation

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3 INTRODUCTION

This statistical analysis plan (SAP) for the final analysis is based on the approved clinical study protocol (CSP), Version 1.0, dated 20 October 2017, approved electronic case report form (eCRF), Version 1.0, dated 12 April 2017, and approved eCRF completion guidelines, Version 1.0, dated 25 May 2017.

This is a Phase 3b, randomized, double-blind, placebo-controlled, single-center, crossover study that includes two 8-week treatment periods separated by an 8-week washout period to evaluate the efficacy of ivacaftor treatment in subjects with CF 6 years of age and older who have a *3849 + 10KB C→T* or *D1152H-CFTR* mutation, [redacted]

This SAP (Methods) documents the planned statistical analyses of efficacy and safety endpoints, [redacted]

Vertex Biometrics will perform the statistical analysis for the final analysis. SAS® Version 9.2 or higher software (SAS Institute, Cary, North Carolina, USA) will be used to generate all statistical outputs (tables, figures, listings, and datasets).

The SAP (Methods) will be finalized and approved prior to the data lock for the final analysis. Any changes made to the SAP Methods after the data lock has occurred will be documented in the clinical study report for this study.

4 STUDY OBJECTIVES

4.1 Primary Objective

To evaluate the efficacy of ivacaftor treatment in subjects with CF 6 years of age and older who have a *3849 + 10KB C→T* or *D1152H CFTR* mutation.

[redacted]

5 STUDY ENDPOINTS

5.1 Efficacy Endpoint

5.1.1 Primary Efficacy Endpoint

- Change from baseline in lung clearance index$_{2.5}$ ($LCI_{2.5}$; calculated as lung volume turnovers required to reach 2.5% of the starting nitrogen [N_2] concentration) through 8 weeks of treatment.

[redacted]

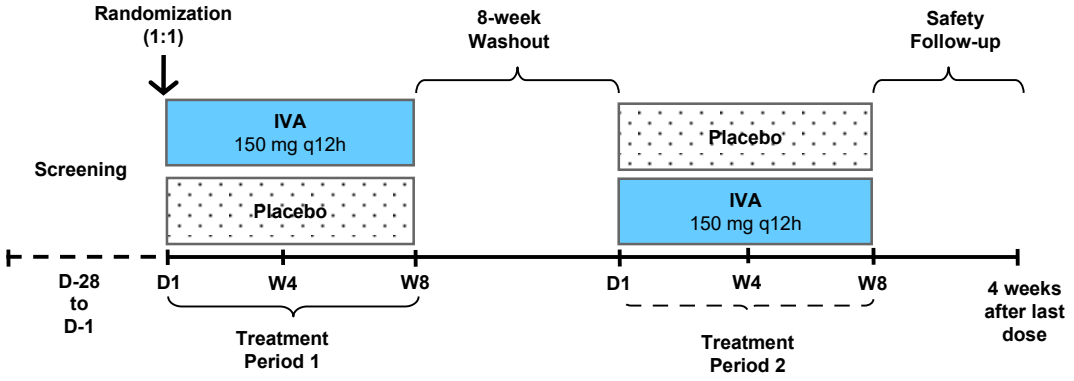
6 STUDY DESIGN

6.1 Overall Design

This is a randomized, double-blind, placebo-controlled, single-center, crossover study that includes two 8-week treatment periods separated by an 8-week washout period (Figure 6-1). There are 7 study visits, not including the Screening Visit. The total study duration for each subject is approximately 32 weeks, including the Screening and the Follow-up periods.

- Sequence 1: ivacaftor (150 mg q12h) in Treatment Period 1; washout; placebo in Treatment Period 2
- Sequence 2: placebo in Treatment Period 1; washout; ivacaftor (150 mg q12h) in Treatment Period 2

Figure 6-1 VX16-770-127 Study Design



6.2 Sample Size and Power

No formal sample size calculation was conducted. The planned sample size of approximately 50 subjects is based on the number of subjects expected to be available for participation.

Assuming an estimated standard deviation (SD) of the paired differences of 1.00 in $LCI_{2.5}$, this available sample size of 50 subjects will produce a 2-sided 95% confidence interval (CI) of the mean treatment difference with precision (margin of error) of 0.28 points. Similarly, the margin of error using a 2-sided 80% CI will be 0.18 points.

6.3 Randomization

An interactive web or voice response system (IXRS) is used to randomize subjects who meet the eligibility criteria to 1 of 2 treatment sequences. Subjects are randomized in a 1:1 ratio, stratifying for age (6 to 11 years, and ≥12 years) and FEV_1 severity (<60%, and ≥60%).

6.4 Blinding and Unblinding

This is a double-blind study.

6.4.1 Blinding

Subjects and all site personnel, including the investigator, site monitor, and study team, will remain blinded to treatment assignments until database lock. The Vertex study team will remain blinded to treatment assignments until all subjects have completed the study. Exceptions are made for the following personnel:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the subject and the fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy serious adverse event (SAE) processing and reporting regulations
- Unblinded statistician who will prepare the final (production) randomization list (this statistician is not part of the study team)
- Vertex IXRS Management for IXRS oversight and system administration
- Vertex Clinical Supply Chain
- The bioanalytical laboratory/vendor personnel managed by Vertex Bioanalysis

Vertex Quality Assurance GCP personnel and all other Vertex Bioanalysis laboratory personnel will be blinded to the treatment assignment.

LCI, [redacted]: During the conduct of the study, the Vertex study team will not have access to the LCI, [redacted] after the morning dose on Day 1. Furthermore, sites, subjects, and their caregivers will not be informed of their study-related LCI, [redacted] results during the study regardless of whether the subject prematurely discontinued treatment.

6.4.2 Unblinding

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

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

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

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

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor will be notified within 24 hours of the unblinding event. The reason and the date of the unblinding will be documented clearly in the subject's study file. Information about the treatment assignment obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with the sponsor (Vertex), contract research organization (CRO), or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS or designee, per Section 13.1.2 of clinical study protocol.

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

7 ANALYSIS SETS

The following analysis sets are defined: All Subjects Set, Full Analysis Set and Safety Set.

7.1 All Subjects Set

The **All Subjects Set** will include all subjects who were randomized or received at least 1 dose of study drug. This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

7.2 Full Analysis Set

The **Full Analysis Set** (FAS) will be defined as all randomized subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug. The FAS will be used to summarize subject demographics and baseline characteristics, and for efficacy [redacted], unless specified otherwise. Subjects will be analyzed according to the treatment they were randomized to.

7.3 Safety Set

The **Safety Set** will include all subjects who received at least 1 dose of study drug. The Safety Set will be used for all safety analyses, unless otherwise specified. Subjects will be analyzed according to the treatment they received.

8 STATISTICAL ANALYSIS

8.1 General Considerations

The treatment sequences will be defined as ivacaftor → placebo and placebo → ivacaftor, and the treatment groups will be defined as ivacaftor and placebo. The results of the statistical analysis will be presented by treatment group, unless specified otherwise.

The Schedule of Assessments is provided in Appendix A. The precision standards for reporting safety and efficacy variables are provided in an internal Biometrics document that specifies the programming rules including the precision for derived variables.

All individual subject data for those randomized or dosed with any amount of study drug will be presented in data listings.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, standard error (SE), median, minimum value (min), and maximum value (max). SE may not be reported for safety summary tables.

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

Baseline value will be defined as follows.

The Study Baseline will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug on Day 1 of Treatment Period 1. The study baseline will be used to summarize demographics, background, and baseline characteristics and for all efficacy analyses.

The Period Baseline will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug on Day 1 of each Treatment Period. For Treatment Period 2, the baseline should be from an assessment measured after the treatment emergent period (described below) for Treatment Period 1. The period baseline will be used for all safety analyses.

For sweat chloride, the study baseline value will be the mean of assessment values on the left and the right arm at the most recent time point prior to the first dose of study drug on Day 1 of the study. If the result from only one of the arms is available then the result from that arm will be considered as baseline.

Absolute change from baseline will be calculated as postbaseline value – baseline value.

Treatment Emergent (TE) Period for Treatment Period 1 (TE Period 1) will correspond to data from the first dose of study drug in Treatment Period 1 to the Safety Follow-up (SFU) visit, if the subject discontinues treatment in Treatment Period 1 or 28 days after the last dose in Treatment Period 1 for subjects who continue to Treatment Period 2 or subjects who discontinue in Treatment Period 1 and do not have an SFU visit. Similarly, the TE period for Treatment Period 2 (TE Period 2) will correspond to data from the first dose of study drug in Treatment Period 2 to the SFU visit or 28 days after the last dose in Treatment Period 2 for subjects who do not have an SFU visit.

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

- In scheduled visit windows per specified visit windowing rules
- In the derivation of baseline and last on-treatment measurements
- In the derivation of maximum and minimum on-treatment values, and maximum and minimum change from baseline values for safety analyses
- In individual subject data listings as appropriate

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix B.

Incomplete/missing data will not be imputed, unless specified otherwise.

Outliers: No formal statistical analyses will be performed to detect or remedy the presence of statistical outliers, unless specified otherwise.

Multiplicity: There will be no multiplicity adjustment for performing multiple hypothesis tests, unless specified otherwise.

8.2 Background Characteristics

8.2.1 Subject Disposition

Subject disposition will be summarized as follows.

The number of subjects in the following categories will be summarized by treatment sequence and overall:

- All Subjects Set (randomized or dosed)
- Randomized
- Full Analysis Set (FAS)
- Safety Set

The number and percentage (based on FAS) of subjects in each of the following disposition categories will be summarized by treatment sequence and overall as follows:

- Completed treatment period 1
- Prematurely discontinued treatment period 1 and the reason for discontinuation
- Completed treatment period 2
- Prematurely discontinued treatment period 2 and the reason for discontinuation
- Completed study (i.e., completed Safety Follow-up Visit)
- Prematurely discontinued the study and the reason for discontinuation

A listing will be provided for subjects who discontinued treatment or who discontinued study with reasons for discontinuation. A randomization listing of subjects will also be provided.

8.2.2 Demographics and Baseline Characteristics

Demographics, medical history and baseline characteristics will be summarized based on the FAS, and presented by treatment sequence and overall.

Demographic data will include the following:

- Age at baseline (in years)
- Sex (female and male)
- 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)

Baseline characteristics will include the following:

- Weight at baseline (kg)
- Height at baseline (cm)
- BMI at baseline (kg/m^2)
- BMI z-score at baseline (subjects <21 years old at screening)
- CFTR genotype for Mutation 1 (3849 + 10KB C→T and D1152H)

Note: For subjects who may have both CFTR mutations, the priority order will be to choose 3849+10KB C→T as allele 1 mutation and D1152H as allele 2 mutation, even though this case is unlikely to occur.

Stratification categories will include the following:

- $ppFEV_1$ at screening (<60 and ≥60)
- Age group at screening (6 - 11 years and ≥12 years)

Disease characteristics will include the following:

- ppFEV$_1$ at baseline (<40, ≥40 to <70, ≥70 to ≤90, >90)
- ppFEV$_1$ at baseline (continuous)
- LCI$_{2.5}$ at baseline (continuous)
- Sweat Chloride at baseline (continuous)
- FEV$_1$ (L) at baseline (continuous)

[redacted]

A summary of medical history will be provided by MedDRA system organ class (SOC) and preferred term (PT) by treatment sequence and overall for the FAS. Further, the CFTR genotype for all mutations for each subject will be provided in an individual subject data listing.

8.2.3 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHODDE) and categorized as follows:

Prior medication: any medication that started before the first dose date of study drug, regardless of when the medication ended.

Concomitant medication: medication continued or newly received on or after the first dose date of study drug through the end of the TE period for Treatment Period 1 or 2.

Post-treatment medication: medication continued or newly received after the TE period for Treatment Period 1 or 2.

A given medication may be classified as follows: prior, concomitant, post-treatment, both prior and concomitant, both concomitant and post-treatment, or prior, concomitant, and post-treatment.

If a medication has a completely missing or partially missing start/stop date and it cannot be determined whether it was taken before the first dose date of study drug, concomitantly, or after the TE period, it will be classified as prior, concomitant, and post-treatment.

Prior medications and concomitant medications, separately, will be summarized descriptively using frequency stables by preferred name. The summary of prior medications will be based on the FAS and presented by treatment sequence and overall. The summary of concomitant medications will be based on the FAS and presented by treatment group.

An individual subject data listing will be provided for all prior medications, concomitant medications and post-treatment medications.

Details for imputing missing or partial start and/or stop dates of medication are described in Appendix C.

8.2.4 Study Drug Exposure

Study drug exposure (in days) will be calculated as: last dose date of study drug – first dose date of study drug + 1 day, regardless of study drug interruption, and will be summarized descriptively by treatment group.

Study drug exposure (in weeks) will be summarized descriptively by the number of subjects (n), mean, SD, SE, median, min, and max. It will also be summarized in categories: ≤2 weeks, >2- ≤4 weeks, >4 - ≤8 weeks, and >8 weeks, using counts and percentages. Additionally, the total study drug exposure, defined as the sum total of the study drug exposure across all subjects (in patient-weeks), will be provided.

Exposure summaries will be based on the Safety Set, and presented by treatment group.

8.2.5 Study Drug Compliance

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

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

Percentage of tablets taken and study drug compliance will be summarized descriptively by the number of subjects (n), mean, SD, SE, median, min, and max. It will also be summarized in categories: <80% and ≥80% using frequency tables.

Percentage of tablets taken and study drug compliance summaries will be based on the FAS, and presented by treatment group.

8.2.6 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 before database lock.

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

- Subject was enrolled in the study despite the violation of inclusion/exclusion criteria
- Subject was less than 80% compliant with study drug based on number of tablets taken
- 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 will be provided in an individual subject data listing. Details of the IPD rules are provided in Appendix D.

8.3 Efficacy Analysis

All efficacy analyses will be based on the FAS and will use the study baseline, unless otherwise specified. Further, all efficacy analyses will be performed according to the treatment to which the subject was assigned in each period. Data for a period will be used provided that the subject received at least one dose of study drug in that treatment period.

The analysis will include all available measurements through the last scheduled on-treatment visit, per the visit windowing rules described in Appendix B.

8.3.1 Primary Efficacy Variable

The primary efficacy variable is the absolute change in $LCI_{2.5}$ (calculated as lung volume turnovers required to reach 2.5% of the starting N_2 concentration) from study baseline through Week 8 in each treatment period.

8.3.1.1 Primary Analysis of the Primary Efficacy Variable

The hypothesis is that the average decrease from study baseline through Week 8 in $LCI_{2.5}$ is greater for ivacaftor versus placebo. A test of the hypothesis will be based on the Bayesian approach to statistical inference. If the posterior probability exceeds 80% that the difference in the average change from study baseline between ivacaftor and placebo is less than zero, then that will be considered as sufficient statistical evidence in favor of the hypothesis, and the study will be considered successful.

The primary analysis will be performed using a Bayesian approach. The change from study baseline to each post-baseline visit through Week 8 in each treatment period will be calculated for each subject and modeled using a repeated measures regression model with mean response for each sequence by treatment period by visit cell modeled as a cell-specific effect with continuous study baseline $LCI_{2.5}$ as a covariate. A UN@CS direct product covariance matrix will be used to model the correlation between the repeated measurements by treatment period and visit within an individual subject. This covariance matrix assumes an unstructured covariance between treatment period-specific repeated measures, and a compound symmetry covariance between visit-specific repeated measures within a treatment period. A non-informative prior distribution (normal distribution with mean = 0 and variance = 10^6) will be assumed for each of the unrestricted cell-specific effects and covariate effect in the model, and a flat distribution (unrestricted for UN covariance parameters and CS covariance parameters) will be assumed for each of the variance-covariance parameters of the covariance matrix.

The average treatment difference will be defined as the mean of the average change in $LCI_{2.5}$ from study baseline through Week 8 for ivacaftor versus placebo. This average treatment difference will be obtained using an appropriate contrast of the cell means by averaging over visits within a period and across sequences, assuming no carryover effect from Treatment Period 1 to Treatment Period 2 due to the 8-week washout period between treatment periods, and will be estimated using the Markov Chain Monte Carlo (MCMC) method via PROC MCMC in SAS. If the model does not converge, a reduced model with a compound symmetry covariance matrix will be used for sequential visits across both treatment periods 1 and 2 within an individual subject. The posterior probability that the average treatment difference is less than zero (lower lung clearance index values are better) will be calculated. Further, the posterior mean of the average treatment difference, with the posterior median, 25th percentile, and 75th percentile will be provided, and the posterior distribution of the average treatment difference will be plotted.

8.3.1.2 Supportive Analysis of the Primary Efficacy Variable

A supportive analysis of the primary efficacy variable will be performed using a frequentist confidence interval estimation approach based on a mixed-effects model for repeated measures (MMRM) with change in $LCI_{2.5}$ from study baseline as the dependent variable. The model will include treatment group, visit (treatment period), treatment group by visit (within treatment period) interaction, and treatment period as fixed effects and subject as a random effect, with the continuous study baseline $LCI_{2.5}$ as a covariate, and will include data from each treatment group and visit through Week 8 in each treatment period. No sequence effect (alias for carryover effect) is included in the model due to the 8-week washout period between the treatment periods. A UN@CS direct product covariance matrix will be used to model the correlation between the repeated measurements by treatment period and visit (within treatment period) within an individual subject. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the F test for fixed effects will be estimated using the Kenward-Roger approximation. If the model does not converge, a reduced model with a compound symmetry covariance matrix will be used for sequential visits across both treatment periods 1 and 2 within an individual subject. Conditional on the observed data and covariates, missing data due to treatment or study discontinuation will be assumed to be missing at random resulting in no imputation performed for missing data.

The least squares (LS) mean and 95% confidence interval (CI) of the average treatment difference through Week 8 will be estimated within MMRM using PROC MIXED in SAS, for both within-treatment and between-treatment. Further, the LS mean and 95% CI of the treatment difference at each post-baseline visit through Week 8 will be provided for both within-treatment and between-treatment.

The LS mean (with 95% CI) of the treatment difference at each post-baseline visit through Week 8 will be plotted by treatment group. In addition, a waterfall plot showing the subject-level placebo-corrected change in $LCI_{2.5}$ from study baseline at Week 8 will be presented for the ivacaftor group.

Further, a descriptive analysis of the change from study baseline will be performed by post-baseline visit through Week 8, for each treatment group.

[redacted]

[redacted]

8.4 Safety Analysis

All safety analyses will be based on data from the TE Period for treatment periods 1 and 2, for all subjects in the Safety Set.

All change from baseline analyses will use the period baseline as the baseline value.

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

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (liver function, amylase, lipase)
- Vital signs
- Physical Examination
- Ophthalmology Examination

All safety data will be summarized by treatment group and overall.

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

8.4.1 Adverse Events

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

Pretreatment AE: any AE that started before the first dose date of study drug

TEAE: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug through the end of the TE period for treatment periods 1 or 2

Post-treatment AE: any AE that worsened (either in severity or seriousness) or that was newly developed beyond the TE period for treatment periods 1 or 2

For AEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs started before or after study treatment in treatment periods 1 or 2, the AEs will be classified as TEAEs.

Details for imputing missing or partial start dates of adverse events are described in Appendix H.

AE summary tables will be presented for TEAEs only, for the TE period for treatment periods 1 and 2, by treatment group and overall, for the following:

- Number of TEAEs (total number of TEAEs only)
- Subjects with any TEAEs
- Subjects with TEAEs by Strongest Relationship
- Subjects with TEAEs by Maximum Severity
- Subjects with TEAEs Leading to Study Drug Discontinuation (Discontinuation of all study drug)
- Subjects with TEAEs Leading to Study Drug Interruption (Interruption of all study drug)
- Subjects with Serious TEAEs
- Subjects with TEAE Leading to Death

Summaries will be presented by MedDRA system organ class (SOC) and preferred term (PT) using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentages of subjects, 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 strongest relationship level in the relationship summaries.

All AEs, including pre-treatment AEs, TEAEs, and post-treatment AEs, will be presented in an individual subject data listing based on the All Subjects Set.

8.4.2 Clinical Laboratory

For the treatment-emergent laboratory assessments, the observed values and change from period baseline values of liver function, amylase and lipase test results will be summarized in SI units at each scheduled visit, by treatment group.

The number and percentage of subjects meeting at least 1 threshold analysis criterion event during the TE period will be summarized by treatment group and overall. The threshold analysis criteria for clinical lab results are provided in Appendix I.

For liver function laboratory tests (ALT, AST, ALP, GGT, and total bilirubin), a scatter plot of the maximum treatment-emergent value versus the period baseline value corresponding to xULN will be presented. Further, a scatter plot of the maximum treatment-emergent value of ALT and AST, separately, versus the maximum treatment-emergent value of total bilirubin corresponding to xULN will also be presented by treatment group.

In addition, a listing containing all individual subject laboratory test results including liver function, amylase and lipase test result values outside the normal reference ranges will be provided. This listing will include data from both scheduled and unscheduled visits.

8.4.3 Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from period baseline values will be summarized by treatment group, at each scheduled visit. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), body temperature (°C), HR (beats per minute), and respiratory rate (breaths per minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE period will be summarized by treatment group and overall. The threshold analysis criteria are provided in Appendix I.

In addition, a listing containing all individual subject vital signs measurements will be provided. This listing will include data from both scheduled and unscheduled visits.

8.4.4 Physical Examination

Abnormal physical examination findings will be presented as an individual subject data listing only.

8.4.5 Ophthalmology Examination (age <18 years at screening)

Ophthalmology examination findings will be presented as an individual subject data listing only.

9 INTERIM AND IDMC ANALYSES

9.1 Interim Analysis

Not applicable.

9.2 IDMC Analysis

Not applicable.

10 REFERENCES

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

[2]Quittner AL, Modi A, Cruz I. Systematic review of health-related quality of life measure for children with respiratory conditions. Pediatr Respir Rev. 2008;9:220-32.

[3]Goss C, Quittner AL. Patient-reported outcomes in cystic fibrosis. Proc Am Thorac Soc. 2007;4:1-9.

[4]Modi AC, Quittner AL. Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis. J Pediatr Psychol. 2003;28(8):535-45.

11 LIST OF APPENDICES

Appendix A: Schedule of Assessments

Table 11-1 Study VX16-770-127: Treatment Period and Follow-up Visit Assessments

	Treatment Period 1			Washout Period	Treatment Period 2			Early Termination of Treatment (ETT)	Safety Follow-up 4 weeks (± 7 days) after last dose of study drug[a]
Event/Assessment	**Day 1**	**Week 4 (± 4 days)**	**Week 8 (± 4 days)**	**8 weeks (± 4 days)**	**Day 1**	**Week 4 (± 4 days)**	**Week 8 (± 4 days)**		
Review of inclusion /exclusion criteria	X								
Randomization	X								
[redacted]									
Meal(s) or snack(s) at site[c]	X	X	X		X	X	X		
Vital signs[d]	X	X	X		X	X	X	X	X
[redacted]									
Physical examination	X		X		X		X	X	X

[a] If the ETT Visit occurs ≥3 weeks after the last dose of study drug, the Follow-up Visit will not be required.

[redacted]

[c] Fat-containing food such as a standard CF high-fat, high-calorie meal or snack will be provided to subjects at the site after all predose assessments have occurred.

[d] Vital signs (blood pressure, pulse rate, respiration rate, and body temperature) will be collected after the subject has been at rest (supine) for 5 minutes. Blood pressure will be measured by sphygmomanometer. Vital sign assessments will be performed before blood draws.

[redacted]

Table 11-1 Study VX16-770-127: Treatment Period and Follow-up Visit Assessments

Event/Assessment	Treatment Period 1			Washout Period	Treatment Period 2			Early Termination of Treatment (ETT)	Safety Follow-up 4 weeks (± 7 days) after last dose of study drug[a]
	Day 1	Week 4 (± 4 days)	Week 8 (± 4 days)	8 weeks (± 4 days)	Day 1	Week 4 (± 4 days)	Week 8 (± 4 days)		
Multiple breath washout[f]	X	X	X		X	X	X		
[redacted]									
Pregnancy test (female subjects of childbearing potential)[h]	X	X	X		X	X	X	X	X
Liver function tests (LFTs)[i]	X		X		X		X	X	X
Amylase and lipase	X		X		X		X	X	X
Ophthalmological examination[j]							X	X	

[f] Multiple breath washout [redacted] will be performed pre-bronchodilator [redacted], and must be performed before dosing.

[redacted]

[h] A urine β-hCG test will be performed at all visits in Treatment Periods 1 and 2 and will be performed before the first dose of study drug on Day 1 of Treatment Periods 1 and 2. A urine β-hCG test will be performed at the ETT visit (as applicable). A serum pregnancy test will be performed at the Safety Follow-up Visit.

[i] ALT, AST, GGT, alkaline phosphatase, and bilirubin

Table 11-1 Study VX16-770-127: Treatment Period and Follow-up Visit Assessments

Event/Assessment	Treatment Period 1			Washout Period	Treatment Period 2			Early Termination of Treatment (ETT)	Safety Follow-up 4 weeks (± 7 days) after last dose of study drug[a]
	Day 1	Week 4 (± 4 days)	Week 8 (± 4 days)	8 weeks (± 4 days)	Day 1	Week 4 (± 4 days)	Week 8 (± 4 days)		
Ivacaftor or placebo dosing	X	X	X		X	X	X		
Concomitant treatments and procedures	----------Continuous from signing of the ICF and Assent (where applicable) through the Safety Follow-up Visit----------								
Adverse events	----------Continuous from signing of the ICF and Assent (where applicable) through the Safety Follow-up Visit----------								

[j] OE is required for subjects who were under 18 years of age at the Screening Visit. OE will be performed either at the Week 8 Visit of Treatment Period 2 or at the ETT Visit. This examination is not required if the subject received study drug for a total of less than 4 weeks.

Appendix B: Analysis Visit Windows for Safety and Efficacy Assessments

Table 11-2 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[a]	Target Treatnent Period Day[b]	Analysis Visit Window (in treatment period days)
Safety Assessment (Treatment Period 1)			
Vital Signs [redacted]	Day 1 (Baseline) Week 4 Week 8	1 29 57	≤1 [2, 43] [44, 71]
Liver Function Tests Amylase Lipase	Day 1 (Baseline) Week 8	1 57	≤1 [2, 71]
Safety Assessment (Treatment Period 2)			
Vital Signs [redacted]	Day 1 (Baseline) Week 4 Week 8 Safety Follow-up	1 29 57 NA	≤1 [2, 43] [44, 71] Nominal visit
Liver Function Tests Amylase Lipase	Day 1 (Baseline) Week 8 Safety Follow-up	1 57 NA	≤1 [2, 71] Nominal visit
Efficacy Assessment (Treatment Period 1)			
[redacted]			
MBW (LCI)	Week 8	57	[44, 71]
[redacted]			
Efficacy Assessment (Treatment Period 2)			
[redacted]			
MBW (LCI)	Week 8	57	[44, 71]
[redacted]			

[a] Visit name is used to report data in tables, listings and figures.

[b] Target day time point per protocol is predose.

Table 11-2 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[a]	Target Treatnent Period Day[b]	Analysis Visit Window (in treatment period days)
[redacted]			

[a]Visit name is used to report data in tables and figures.

[b]Target day time point is predose.

Note:

The analysis visit windows will be applied using the following rules for both scheduled and unscheduled visits:

1. If no numerical measurement is available within a visit window, the measurement will be considered missing for the visit.
2. If there is more than 1 numerical measurement available within the same visit window, use the following rules:
   a. For efficacy parameters: if there are multiple measurements within a visit window, the measurement at the scheduled visit will be used. Otherwise,
      i. If there are no measurements at the scheduled visit, then the measurement closest to the target day will be used; or
      ii. If there are multiple measurements with the same distance to the target day, the latest measurement will be used.
   b. For safety parameters: if there are multiple measurements within a visit window,
      i. The measurement closest to the target day will be used; or
      ii. If there are multiple measurements within the same distance from the target day, the latest measurement will be used.
      iii. For tables of the extreme lab measurement based on ULN or LLN, convert the lab measurements into times of ULN or LLN first, and then select the extreme measurement.

Derived Variables:

1. Age (in years) at first dose date

Obtain age at screening (in days) in yy mm format (e.g., 24 years, 6 months) from screening vital signs page, and add 0.5 month to convert to days.

Obtain screening date from Date of Visit (DOV) page.

Then age (in years) at first dose date = integer part of {[(first dose date-screening date) in days + age at screening (in days)]/365.25}.

Correspondingly, age (in months) at first dose date = integer part of 12*{[(first dose date-screening date) in days + age at screening (in days)]/365.25}.

2. Age (in years) at post-baseline visit (for use in calculation of percent predicted spirometry variables)

Table 11-2 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[a]	Target Treatnent Period Day[b]	Analysis Visit Window (in treatment period days)
Age (in years) at post-baseline visit = integer part of {[(post-baseline visit date – screening date) in days + age at screening (in days)]/365.25} 3. Missing First Dose Date or Last Dose Date If the first dose date is missing, use Day 1 visit date. If the last dose date is missing at final analysis, use maximum of Early Treatment Termination (ETT) visit date and last study drug administration date from EX SDTM domain. When a subject is lost to follow up without ETT, impute the last dose date as the last on-treatment visit date.			

Appendix C: Imputation Rules for Missing Prior/Concomitant Medication Dates

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date (in practical, use Jan. 01, 2000 to impute).
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last day of the month.
    b. If DAY and Month are both missing, use the last day of the year.
    c. If DAY, Month and year are all missing, assign 'continuing' status to stop date (in practical, use Dec. 31, 2050 to impute).

In summary, the prior, concomitant in TE Period 1or post categorization of a medication in TE Period 1 is described in Table 11-3 below.

Table 11-3 Prior, Concomitant, and Post Categorization of a Medication in TE Period 1

	Medication Stop Date		
Medication Start Date	**< Start date of TE Period 1**	**≥ Start date of TE Period 1 and ≤ End Date of TE Period 1**	**> End Date of TE Period 1 and < Start date of TE Period 2**
< Start date of TE Period 1	P	PC1	PC1A1
≥ Start date of TE Period 1and ≤ End date of TE Period 1	-	C1	C1A1
> End date of TE Period 1	-	-	A1

P: Prior; C1: Concomitant in Treatment Period 1; A1: Post in Treatment Period 1

A similar categorization is described in Table 11-4 below for TE Period 2.

Table 11-4 Concomitant, and Post Categorization of a Medication in TE Period 2

	Medication Stop Date	
Medication Start Date	**≥ Start date of TE Period 2 and ≤ End Date of TE Period 2**	**> End Date of TE Period 2**
≥ Start date of TE Period 2 and ≤ End date of TE Period 2	C2	C2A2
> End date of TE Period 2	-	A2

Appendix D: Important Protocol Deviation Programming Rules (Based on the Clinical Database)

Important programmable protocol deviations before first dose

1. Inclusion criteria:
   a) I3: Six years of age and older and ≥25 kg on the date of the ICF.
   b) I6: FEV_1 ≥40% of predicted and ≤105% of predicted at screening, based on the Global Lung Function Initiative (GLI)-2012 multi-ethnic all-age reference equations.
2. Exclusion criteria:
   a) E4: Any of the following abnormal laboratory values at the Screening Visit:
      - Hemoglobin <10 g/dL
      - Alanine aminotransferase (ALT) or AST >5 × upper limit of normal (ULN)
      - Bilirubin >2 × ULN
      - Glomerular filtration rate ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation in subjects <18 years of age and the Modification of Diet in Renal Disease equation in subjects ≥18 years of age).

Appendix E: Details of GLI Equations for Calculating ppFEV$_1$

Percent predicted values will be calculated for parameters of FEV$_1$, [redacted] using the Quanjer GLI-2012 Regression Equations and Lookup Tables.

The regression equations and lookup tables required to implement the Quanjer GLI-2012 predicted values are available in:

Quanjer GLI-2012 Regression Equations and Lookup Tables. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 7 April 2013. Available at:

http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/quanjer-gli-2012-regression-equations-and-lookup-tables.aspx.

Accessed March 13, 2017.

The instructions and tools on how to implement the Quanjer GLI-2012 equations are:

Implementing GLI-2012 regression equations. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 19 July 2015. Available at:

http://www.ers-education.org/guidelines/global-lung-function-initiative/gli-2012-explained.aspx.

Accessed March 13, 2017 .

GLI-2012 - SAS Macro. Sanja Stanojevic. Version 2, 7 April 2013. Available at:

http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/sas-macro.aspx

Accessed March 13, 2017.

Appendix H: Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined as follows.

- **If only Day of AE start date is missing:**
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then
        - if AE start year and month are equal to the month and year of first dose date of the Treatment Period, then impute the AE start day as the day of first dose date of the Treatment Period;
        - else impute the AE start day as 1.
    - else 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 the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then
        - if AE start year is equal to the year of first dose date of the Treatment Period, then impute the AE start month and day as the month and day of first dose date of the Treatment Period;
        - else impute the AE start month as January and day as 1.
    - else impute the AE start month as January and 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.
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then the AE will be considered as TEAE for the Treatment Period.
    - else the AE will be considered as a pretreatment AE.

Imputation rules for partial AE end date are defined as follows:

If partial end date, then impute as min (the last day of the month, end of study) if day is missing, or min (Dec, end of study) if month is missing.

Appendix I: Criteria for Threshold Analysis

Table 11-9 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Clinical Chemistry (LFT)		
ALT	>ULN - ≤3xULN >3 - ≤ 5xULN >5 - ≤ 8xULN >8 - ≤ 20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
AST	>ULN - ≤3xULN >3 - ≤ 5xULN >5 - ≤ 8xULN >8 - ≤ 20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
ALT or AST	(ALT>ULN - ≤ 3xULN) or (AST>ULN - ≤ 3xULN) (ALT>3 - ≤ 5xULN) or (AST>3 - ≤ 5xULN) (ALT>5- ≤ 8xULN) or (AST>5 - ≤ 8xULN) (ALT>8 - ≤ 20xULN) or (AST>8 - ≤ 20xULN) ALT>20xULN 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 Jul 2009.
Total Bilirubin	>ULN - ≤ 1.5xULN >1.5 – ≤ 2xULN >2 – ≤ 3xULN >3 – ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
Direct Bilirubin	>ULN - ≤ 1.5xULN >1.5 – ≤ 2xULN >2 – ≤ 3xULN >3 – ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
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.

Table 11-9 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
GGT	>ULN - ≤ 2.5xULN >2.5 – ≤ 5.0xULN >5.0 – ≤ 20.0xULN >20.0xULN	CTCAE grade 1-4
Clinical Chemistry (NON-LFT)		
Amylase	>1 - ≤ 1.5xULN >1.5 - ≤ 2xULN >2 - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Lipase	>ULN - ≤ 1.5xULN >1.5 - ≤ 2xULN >2 - ≤ 5xULN >5xULN	Criteria based upon CTCAE

Table 11-10 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
HR	Bradycardia <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	Per HV grade 2, 3, plus shift change
	Tachycardia >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	Per HV grade 1, 2, 3, plus shift change

Table 11-10 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
SBP increased		809/770 analyses
	>140 mmHg	
	>160 mmHg	
	>10 mmHg increase from baseline	
	>20 mmHg increase from baseline	
	>140 mmHg and >10 mmHg increase from baseline	
	>140 mmHg and >20 mmHg increase from baseline	
	>160 mmHg and >10 mmHg increase from baseline	
	>160 mmHg and >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	

Table 11-10 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
DBP increased		
	>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	
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 ≥5% increase from baseline ≥10 % increase from baseline ≥ 20% increase from baseline	CTCAE grade 1-3
	Weight loss ≥5% decrease from baseline ≥10 % decrease from baseline ≥ 20% decrease from baseline	CTCAE grade 1-3