VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX16-152-102 Version 3.0 (Final Analysis)

A Phase 2, Randomized, Double blind, Controlled Study to Evaluate the Safety of VX-152 Combination Therapy in Adults With Cystic Fibrosis

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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 3.0, dated 14 Apr 2017, approved electronic case report form (eCRF), Version 1.0, dated 28 Oct 2016, and approved eCRF completion guidelines, Version 1.0, dated 24 Nov 2016. This SAP will also be used to perform interim analyses (IAs) that may be performed for each cohort after 50% or 100% subjects in the cohort have completed the Day 15 Visit or Day 29 Visit.

This is a Phase 2, 2-part, randomized, double blind, placebo and VX-661/ivacaftor (IVA) controlled, parallel group, multicenter study designed to evaluate the safety of VX-152 in TC with VX-661 and IVA.

This SAP (Methods) documents the planned statistical analyses of efficacy endpoints and safety endpoints.

Vertex Biometrics will perform the statistical analysis for each IA and the final analysis. SAS® Version 9.4 (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 unblinding of the data for the first IA that involves model-based analyses. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP prior to the clinical database lock for the final analysis. Any changes made to the SAP Methods after the clinical database lock has occurred will be documented in the clinical study report for this study.

4 STUDY OBJECTIVES

4.1 Primary Objective

- To evaluate the safety and tolerability of VX-152 in triple combination (TC) with VX-661 and IVA in adults with cystic fibrosis (CF)

4.2 Secondary Objectives

- To evaluate the pharmacodynamic (PD) effect of VX-152 in TC with VX-661 and IVA on CFTR function
- To evaluate the efficacy of VX-152 in TC with VX-661 and IVA
- To evaluate the pharmacokinetics (PK) of VX-152 when administered in TC with VX-661 and IVA
- To evaluate the PK of VX-661, IVA, and their respective metabolites when administered with VX-152

5 STUDY ENDPOINTS

5.1 Efficacy Endpoint

5.1.1 Primary Efficacy Endpoint

- Absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) from baseline at Day 15 (Parts 1 and 2) and through Day 29 (Part 2, Cohort 2B only)

5.1.2 Secondary Efficacy Endpoints

- Absolute change in sweat chloride concentrations from baseline at Day 15 (Parts 1 and 2) and through Day 29 (Part 2, Cohort 2B only)
- Relative change in ppFEV1 from baseline at Day 15 (Parts 1 and 2) and through Day 29 (Part 2, Cohort 2B only)
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline at Day 15 (Parts 1 and 2) and at Day 29 (Part 2, Cohort 2B only)

[redacted]

5.2 Safety Endpoints

Safety and tolerability assessments are evaluated via the following:

- adverse events (AEs)
- clinical laboratory values
- standard 12-lead electrocardiograms (ECGs)
- vital signs
- pulse oximetry

6 STUDY DESIGN

6.1 Overall Design

This is a Phase 2, 2-part, randomized, double blind, placebo and VX-661/IVA controlled, parallel group, multicenter study designed to evaluate the safety of VX-152 in TC with VX-661/IVA.

Up to approximately 72 subjects with CF are planned for enrollment: up to approximately 36 subjects in each of Part 1 (*F508del*/MF genotype) and in Part 2 (*F508del*/*F508del* genotype).

Parts 1 and 2 will enroll multiple cohorts, with each cohort evaluating 1 dose level of VX-152 as part of TC with VX-661/IVA (100 mg qd/150 mg q12h). Each cohort will enroll up to approximately 12 subjects in Part 1 and Part 2 Cohort 2A and up to approximately 24 subjects in Part 2 Cohort 2B. Subjects in all cohorts will be randomized 3:1 (active TC:

comparator). Triple placebo will be the comparator in Part 1, and VX-661/IVA will be the comparator in Part 2.

Up to 3 cohorts are planned for Part 1 (Cohorts 1A, 1B, and 1C). Up to 2 cohorts are planned for Part 2 (Cohorts 2A and 2B). The doses of VX-152 planned for evaluation are 100 mg q12h in Cohort 1A, 200 mg q12h in Cohorts 1B and 2A, and 300 mg q12h in Cohorts 1C and 2B. The dose of VX-152 may be adjusted to be lower or the same as the dose level evaluated in the previous cohort.

The actual number of cohorts enrolled in each part may be modified based on emerging safety and PK data. Blinded reviews of safety and available PK data will be conducted by the Vertex study team and lead investigator(s) on an ongoing basis.

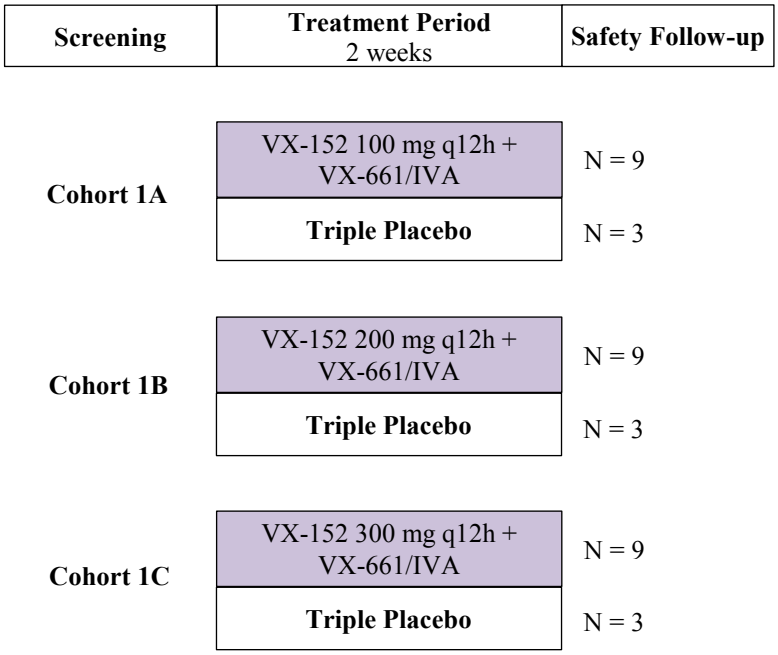
Cohorts will initiate dosing as follows:

- Cohort 1A will initiate dosing first.
- Cohorts 1B and 2A may initiate dosing if supported by blinded review of safety and available PK data after all subjects in Cohort 1A complete the Day 15 Visit.
- Cohorts 1C and 2B may initiate dosing if supported by blinded review of safety and available PK data after any of the following has occurred:
    - All subjects in Cohort 1B complete the Day 15 Visit.
    - All subjects in Cohort 2A complete the Day 15 Visit.
    - At least 12 subjects across Cohorts 1B and 2A complete the Day 15 Visit.

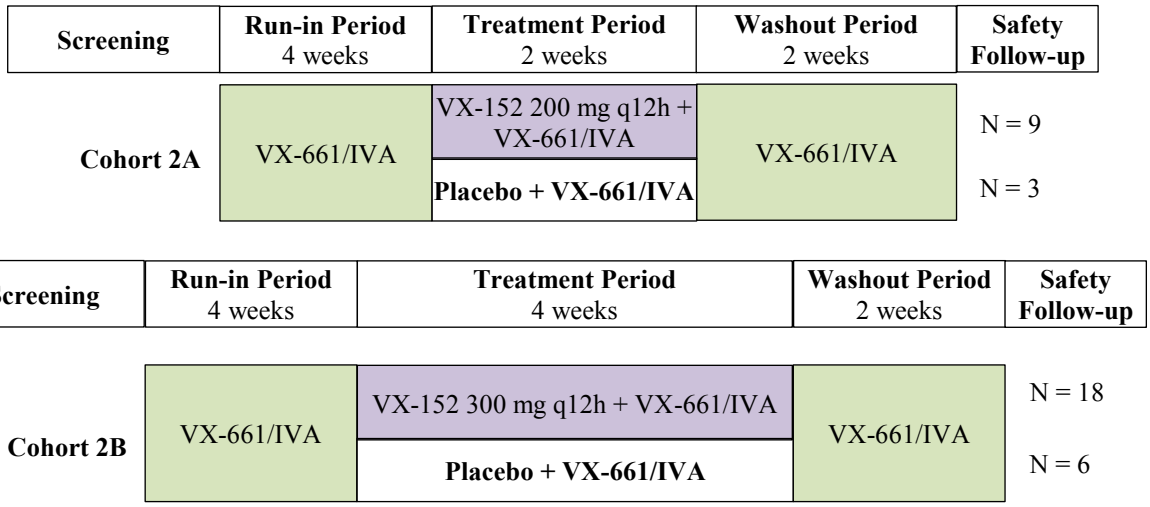
A schematic of the study design (including the doses of VX-152, VX-661, and IVA to be evaluated) is shown in Figure 6-1.

Figure 6-1 Schematic of the Study Design

Part 1: *F508del*/MF (up to ~12 subjects per cohort; randomized 3:1)



Part 2: *F508del*/*F508del* (up to ~12 subjects in Cohort 2A, up to ~24 subjects in Cohort 2b; randomized 3:1)



Notes: Schematic is not drawn to scale. The actual number of cohorts enrolled in each part may be modified based on emerging safety and PK data. The planned doses of VX-152 are shown in the figure but may be adjusted to be lower or the same as the dose level evaluated in the previous cohort. VX-661 will be administered 100 mg qd. IVA will be administered 150 mg q12h.

6.2 Sample Size and Power

6.2.1 Primary Objectives

The primary objective of the study is the evaluation of safety and tolerability of VX-152 in TC with VX-661/IVA. The sample size calculations described below are deemed adequate to evaluate the safety objective of the study, based on clinical and statistical considerations.

6.2.1.1 Safety and Tolerability

The primary safety endpoint is the incidence of AEs. Up to approximately 72 subjects are planned to be enrolled in the study with up to 36 subjects receiving VX-152 in TC with VX-661/IVA for 2 weeks (Part 1 and Part 2, Cohort 2A), and 18 subjects receiving VX-152 in TC with VX-661/IVA for 4 weeks (Part 1 and Part 2, Cohort 2B). The sample size for each treatment group in Parts 1 and 2 will provide sufficient data for a descriptive analysis of AEs. Table 6-1 provides the probability of observing an AE in at least 1 subject based on a sample size of 9 or 18 subjects per TC treatment group and AE incidences ranging from 5% to 15%. The probability calculations are based on a binomial model using the probability calculator in the PASS software package (Version 11.0).

Table 6-1 Probability of Observing an Adverse Event

	Number of Subjects in TC Treatment Group [a]	
AE Incidences[a]	**9**	**18**
5%	37%	60%
10%	61%	85%
15%	77%	95%

[a] AE incidences are based on 2 weeks of treatment in 9 subjects for Part 1 and Part 2 (Cohort 1A), and 4 weeks of treatment in 18 subjects for Part 2, Cohort 2B.

6.2.2 Secondary Objectives

The secondary objectives of the study include the evaluation of the PD effect of VX-152 in TC with VX-661/IVA on sweat chloride concentrations, and the evaluation of the efficacy of VX-152 in TC with VX-661/IVA.

6.2.2.1 Pharmacodynamic Effect

The absolute change from baseline at Day 15 in sweat chloride concentrations is a secondary endpoint used to evaluate the PD objective of the study. In Part 1, a test for a decreasing dose-response trend between placebo and the TC dose groups will be performed using a multiple comparisons procedure (MCP). The procedure consists of testing the null hypothesis of a non-decreasing dose-response trend versus a decreasing trend using the 1-sided maximum *t*-statistic that controls the type I error at alpha = 5%. The procedure requires a family of candidate dose-response models to be prespecified, that covers the range of plausible and diverse dose-response profiles.

The candidate models that best describe the expected decreasing dose-response profile of the TC groups compared to placebo include a linear model, a maximum effect (E_{max}) model, and a sigmoid E_{max} model. The contrasts (i.e., linear combinations of the treatment group means

at Day 15) selected to perform the MCP and that capture the shape of these candidate models are described in Table 6-2 below.

Table 6-2 Contrast Coefficients for the Multiple Comparisons Procedure in Part 1

Candidate Model	Placebo	Cohort 1A Dose	Cohort 1B Dose	Cohort 1C Dose
Linear	3.0	1.0	-1.0	-3.0
E_{max}	3.0	-1.0	-1.0	-1.0
Sigmoid E_{max}	1.0	1.0	-1.0	-1.0

Note: Contrast coefficients are presented for 2 TC dose groups and placebo.

Table 6-3 provides the power to detect a dose-response trend with the MCP procedure for 3 different expected dose-response profiles with 9 subjects assigned to placebo, 9 subjects assigned to TC in Cohort 1A, 9 subjects assigned to TC in Cohort 1B, and 9 subjects assigned to TC in Cohort 1C for a total sample size of 36 subjects in Part 1 (based on 5000 simulations for each profile using the R software package MCPMod [Version 1.0-8]).

Table 6-3 Power to Detect a Decreasing Dose-response Trend Based on Change From Baseline in Sweat Chloride in Part 1

	Mean Change From Baseline in Sweat Chloride				
Candidate Model	Placebo	Cohort 1A Dose	Cohort 1B Dose	Cohort 1C Dose	Power
Linear	0	-12	-16	-20	94%
E_{max}	0	-20	-20	-20	98%
Sigmoid E_{max}	0	0	-20	-20	>99%

Note: A 1-sided maximum *t*-statistic with a sample size of 36 subjects in Part 1 assigned to TC in Cohort 1C, TC in Cohort 1B, TC in Cohort 1A, and placebo at a ratio 1:1:1:1 was used for power calculations. An SD change from baseline in sweat chloride of 13 mmol/L was used for power calculations.

Table 6-4 provides the power to reject the null within-group hypothesis of no decrease in the mean absolute change from baseline for sweat chloride at Day 15 for the TC treatment groups in Parts 1 and 2 with a sample size of 9 or 18 subjects per treatment group. The power calculations are based on a 1-sided 1-sample *t*-test at alpha = 5% using the software package PASS (Version 11.0), assuming a mean change of -10 to -20 mmol/L and an SD of 13 mmol/L in the absolute change from baseline for sweat chloride.

Table 6-4 Power for Within-group Decrease for Mean Absolute Change From Baseline in Sweat Chloride

Mean Absolute Change From Baseline in Sweat Chloride (mmol/L)	Number of Subjects per Treatment Group[a]	
	9	18
-10	68%	93%
-15	93%	>99%
-20	>99%	>99%

Note: An SD of 13 mmol/L for the absolute change from baseline in sweat chloride was used for power calculations.

[a] Applies to Parts 1 and 2.

6.2.2.2 Efficacy

The absolute change from baseline in $ppFEV_1$ at Day 15 is a secondary endpoint used to evaluate the efficacy objective of the study. Table 6-5 provides the power to reject the null within-group hypothesis of no increase in the mean absolute change from baseline for $ppFEV_1$ at Day 15, for the TC treatment groups in Parts 1 and 2 with a sample size of 9 or 18 subjects per treatment group. The power calculations are based on a 1-sided 1-sample *t*-test at alpha = 5% using the software package PASS (Version 11.0), assuming an absolute mean change of 3 to 7 percentage points and an SD of 8 percentage points in the absolute change from baseline for $ppFEV_1$.

Table 6-5 Power for Within-group Increase for Mean Absolute Change From Baseline in $ppFEV_1$

Mean Absolute Change From Baseline in $ppFEV_1$	Number of Subjects per Treatment Group[a]	
	9	18
3%	27%	45%
5%	53%	82%
7%	77%	97%

Note: An SD of 8 percentage points for the absolute change from baseline in $ppFEV_1$ was used for power calculations.
[a] Applies to Parts 1 and 2.

6.3 Randomization

Approximately 12 subjects or 24 subjects (Part 2, Cohort 2B) will be randomized in the ratio 3:1 to TC versus comparator in each cohort. An interactive web response system (IWRS) will be used to assign subjects to treatment. The randomization code lists was produced by [redacted]

6.4 Blinding and Unblinding

This will be a double-blind study.

6.4.1 Blinding

All subjects, site personnel (including the investigator, the site monitor, and the study team), and the Vertex study team will be blinded to the treatment codes with the exception of the following:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the subject and her 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 preparing the final (production) randomization list who is not part of the study team

- Vertex IWRS Manager
- Vertex Clinical Supply Chain
- IDMC
- Vendor performing the interim analyses and preparing the unblinded analysis for the ongoing reviews of efficacy and safety data, and a limited Vertex team not involved in the conduct of the study
- Vendor analyzing PK samples and Vertex Bioanalytical staff (non-study team) reviewing raw data from vendor
- Vertex Modeling and Simulations personnel or vendor conducting the population PK and PK/PD analyses
- Vertex medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time

Sweat Chloride and Spirometry Blinding: During the conduct of the study, the Vertex study team will not have access to the spirometry results after the morning dose on Day 1. Furthermore, sites, subjects, and their parents/caregivers/companions should not be informed of their study-related sweat chloride and spirometry results during the Treatment Period regardless of whether the subject has prematurely discontinued treatment.

A limited Vertex team not involved in the conduct of the study will be unblinded to results of the interim analyses and will have access to safety, efficacy, and PD data for the purpose of conducting ongoing reviews of safety and efficacy data for planning and enabling clinical development, regulatory, and chemistry, manufacturing, and controls (CMC) decisions.

The Vertex study team and lead investigator(s) will also conduct blinded reviews of all available safety and PK data after all subjects within a cohort complete the Day 15 Visit to make decisions about dose selection for potential subsequent cohorts.

When an interim analysis is performed after all subjects in 1 part have completed the Safety Follow-up Visit, results from that part will be unblinded for full review by the Vertex study team.

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 the 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 in the Treatment Period. The FAS will be used to summarize subject demographics and baseline characteristics and for all PD and efficacy analyses, unless specified otherwise.

7.3 Safety Set

Part 1:

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.

If a subject received at least 1 dose of the higher VX-152 dose, then the subject will be analyzed in the treatment group with the highest VX-152 dose in the order of triple placebo,

VX-152 100mg + VX-661/IVA, VX-152 200mg + VX-661/IVA, and VX-152 300mg + VX-661/IVA.

Part 2:

The **Safety Set for the Run-in Period** will include all subjects who received at least 1 dose of study drug in the Run-in Period. This Safety Set will be used for individual subject data listings for the Run-in Period, unless specified otherwise.

The **Safety Set for the Treatment Period** will include all subjects who received at least 1 dose of study drug in the Treatment Period. This Safety Set will be used for all safety analyses for the Treatment Period, unless specified otherwise.

If a subject received at least 1 dose of the higher VX-152 dose, then the subject will be analyzed in the treatment group with the highest VX-152 dose in the order of placebo + TEZ/IVA, VX-152 200mg + VX-661/IVA, and VX-152 300mg + VX-661/IVA.

The safety analysis will focus on the Safety Set for the Treatment Period only, unless otherwise specified.

8 STATISTICAL ANALYSIS

8.1 General Considerations

The analysis will be performed for each part, and presented by treatment group, unless specified otherwise. The treatment groups are defined as follows:

- Part 1: *F508del*/MF genotype group
    - VX-152 100mg q12h + VX-661/IVA, VX-152 200mg q12h + VX-661/IVA, VX-152 300mg q12h + VX-661/IVA, and placebo, with VX-661 component administered as 100 mg qd and IVA component administered as 150 mg q12h.
- Part 2: *F508del*/*F508del* genotype group
    - VX-152 200mg q12h + VX-661/IVA, VX-152 300mg q12h + VX-661/IVA, VX-661/IVA, VX-661/IVA from Cohort 2A and VX-661/IVA from Cohort 2B, with VX-661 component administered as 100 mg qd and IVA component administered as 150 mg q12h.

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, unless otherwise specified, 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 the Treatment Period. For ECG, baseline will be defined as the most recent non-missing measurement (or the average of triplicate measurements, if the most recent non-missing measurement is obtained in triplicate), before the first dose of study drug on Day 1 of the Treatment Period.

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

Relative change from baseline will be calculated as (postbaseline value – baseline value)/baseline value.

Treatment-emergent (TE) period for Part 1 will include the time from the first dose of study drug in the Treatment Period to the Safety Follow-up (SFU) Visit, or 28 Days after the last dose of study drug for subjects who do not complete the SFU Visit.

For Part 2, the TE period will be defined separately for the Run-In Period, and the Treatment Period:

- The TE period for the Run-in Period will include the time from the first dose of study drug in the Run-in Period to: (1) the last day prior to the first dose of study drug in the Treatment Period for subjects who complete the Run-in Period and continue to the Treatment Period, or (2) the SFU Visit for subjects who did not continue to the Treatment Period and have an SFU Visit, or (3) 28 days after the last dose of study drug in the Run-in Period for subjects who do not have an SFU Visit (e.g., subjects who do not meet the criteria to enter the Treatment Period and re-enter Study 661-110). Only data collected up to the end of study for a subject will be included in analysis.
- The TE period for the Treatment Period will include the first dose of study drug in the Treatment Period to: (1) the SFU Visit, or (2) 28 days after the last dose of study drug for subjects who do not have an SFU Visit (e.g. subjects whose Early Treatment Termination (ETT) Visit occurs 3 weeks or later following the last dose of study drug and the ETT visit replaces the SFU visit, or who leave the study early and re-enter Study 661-110). Only data collected up to the end of study for a subject will be included in analysis.

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/last on-treatment measurements.
- In the derivation of maximum/minimum on-treatment values and maximum/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.

Spirometry ($ppFEV_1$) will be used for both efficacy and safety purposes. For efficacy analysis, the assessments will follow the visit windowing rules for efficacy. For safety analysis, the assessments at 5 hours post-dose on nominal days 1 and 15 will be used.

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

For the Treatment Period in Parts 1 and 2, subject disposition will be summarized as described below.

The number of subjects in the following categories will be summarized by treatment group and overall for each part, as applicable:

- All Subjects Set
- Randomized
- Full Analysis Set (FAS)
- Safety Set (For Part 2, this is the Safety Set for the Treatment Period)

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

- Completed study drug treatment
- Prematurely discontinued treatment and the reason for discontinuation (i.e. discontinued all study drugs)
- Completed study (i.e., completed Safety Follow-up Visit or completed all study drug and re-entered Study 661-110 without Safety Follow-up per protocol)
- Prematurely discontinued the study and the reason for discontinuation

For the Run-in Period in Part 2, a separate disposition table will be provided with the following categories:

- Safety Set for the Run-in Period
- Enrolled but not dosed in the Run-in Period
- Completed treatment in the Run-in Period (i.e., completed randomization)
- Prematurely discontinued treatment during the Run-in Period and the reason for treatment discontinuation (i.e., discontinued all study drugs in the Run-in Period)
- Prematurely discontinued the study during the Run-in Period and the reason for study discontinuation

A listing will be provided by part, for subjects who discontinued treatment (including the Run-in Period in Part 2) or who discontinued study with reasons for discontinuation. A randomization listing of subjects will also be provided, by part.

8.2.2 Demographics and Baseline Characteristics

Demographics, medical history and baseline characteristics will be summarized based on the FAS, and presented by treatment group and overall, for each part, as applicable.

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 (kg)
- Height (cm)
- BMI (kg/m^2)

Disease characteristics will include the following:

- $ppFEV_1$ at baseline (<40, ≥ 40 to <70, ≥ 70 to ≤ 90, >90)
- $ppFEV_1$ at baseline (continuous)
- Sweat Chloride at baseline (continuous)
- FEV_1 (L) at baseline (continuous)
- CFQ-R Respiratory Symptoms domain at baseline (continuous)
- Prior use of dornase alfa before first dose of study drug (Yes, No)
- Prior use of inhaled antibiotic before first dose of study drug (Yes, No)
- Prior use of any bronchodilator before first dose of study drug (Yes, No)
- Prior use of any inhaled bronchodilator before first dose of study drug (Yes, No)
- Prior use of any inhaled hypertonic saline before first dose of study drug (Yes, No)
- Prior use of any inhaled corticosteroids before first dose of study drug (Yes, No)
- Infection with Pseudomonas aeruginosa at baseline (Positive, Negative)

Medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT) based for the FAS. In addition, the number of subjects reported to have had positive cultures for respiratory pathogens in 2 years prior to screening will be summarized for the FAS.

8.2.3 Prior and Concomitant Medications

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

For Part 1:

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.

Post-treatment medication: medication continued or newly received after the TE period.

For Part 2:

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

Concomitant medication during the Run-in Period: medication continued or newly received on or after the first dose date of study drug during the Run-in Period through the end of TE period for the Run-in Period.

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

Post-treatment medication: medication continued or newly received after the TE period.

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. Concomitant for Part 2 can be concomitant during the Run-in Period, concomitant during the Treatment Period, or both.

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 will be summarized descriptively using frequency tables by preferred name.

Summaries of medications will be based on the FAS, and presented by treatment group and overall for each part.

Post-treatment medications will be listed only.

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. Study drug exposure will be summarized for the overall study drug period,

which includes the Run-in Period, Treatment Period and Washout Period for Part 2, and the Treatment Period for Part 1. Further, study drug exposure for the combined Treatment Period and Washout Period in Part 2 will also be summarized descriptively.

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- ≤6 weeks and >6 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 and overall, for each part. For Part 2, exposure summaries will be based on the Safety Set for the Treatment Period.

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)]. A study drug interruption on a given day will be determined by an interruption of all drugs on that day.

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.

For all parts, study drug compliance will be summarized for the Treatment Period only. Similarly, for all parts, percentage of tablets taken will be summarized for the Treatment Period only.

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

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
- 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 described in this section will be based on the FAS, unless otherwise specified. The placebo groups will be pooled across all cohorts in Part 1. The TEZ/IVA groups of varying durations during the Treatment Period (2 weeks and 4 weeks) will be kept separate in Part 2, unless specified otherwise. The analysis will include all available measurements through the last scheduled on-treatment visit including measurements after treatment discontinuation, per the visit windowing rules described in Appendix B. The post-dose measurements on the same day will not be used for any model-based analyses.

8.3.1 Primary Efficacy Variable

The primary efficacy variable is the absolute change from baseline for percent predicted FEV_1 at Day 15 in Part 1 and Part 2 Cohort 2A, and through Day 29 in Part 2 Cohort 2B.

The percent predicted FEV_1 is the ratio of FEV_1 (L) to the predicted FEV_1 (L), expressed as a percentage. The predicted FEV_1 will be calculated using the Quanjer GLI-2012 Regression Equations and Lookup Tables, adjusting for age, height, sex and geographic region. Details are provided in Appendix E.

8.3.1.1 Primary Analysis of the Primary Efficacy Variable

The null hypothesis to be tested is that the mean absolute change from baseline in percent predicted FEV_1 ($ppFEV_1$) is not greater than zero for VX-152 in triple combination (TC) with VX-661/IVA at Day 15 in Part 1 and Part 2 Cohort 2A and through Day 29 in Part 2 Cohort 2B.

Part 1:

The primary analysis will be performed using a mixed-effects model for repeated measures (MMRM) with change from baseline in $ppFEV_1$ as the dependent variable. This MMRM analysis will include all treatment groups within Part 1, including placebo, VX-152 100mg, VX-152 200mg and VX-152 300mg. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects, with the continuous baseline ppFEV1 as a covariate, and will include all data from each treatment group and visit up to Day 15. 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. A compound symmetry covariance structure will be used to model the within-subject errors. Conditional on the observed data and covariates, missing $ppFEV_1$ data due to treatment or study discontinuation will be assumed to be missing at random; consequently, no imputation of missing data will be performed.

The adjusted means and 95% confidence intervals (CI) of the treatment effect for each triple combination at Day 15, with a 1-sided *P* value, will be estimated within MMRM using PROC MIXED in SAS, for all within-treatment and between-treatment comparisons. Contrasts based on the fixed effects in the model, defined at the baseline covariate mean for the combined treatment groups using unique subjects in the FAS who have at least one post-baseline measurement through Day 15, will be used to estimate the treatment effect at Day 15, with the corresponding 1-sided *P* value for the 1-sided hypothesis test.

Further, the adjusted mean and the 2-sided 95% CI of the treatment difference for within-group and between-group comparisons at each post-baseline visit up to Day 15 will be provided.

In addition, descriptive analyses of the change from baseline will be performed for all treatment groups by post-baseline visit.

The adjusted mean (with 95% CI) obtained from the MMRM analysis at each post-baseline visit through Day 15 will also be plotted by treatment group. In addition, a waterfall plot showing the subject-level absolute change in ppFEV1 at Day 15 will be presented, by treatment group.

Part 2:

A similar MMRM with change from baseline in $ppFEV_1$ as the dependent variable will be performed separately for each cohort in Part 2. The MMRM analysis will include VX-661/IVA and VX-152 200mg for Cohort 2A, and VX-661/IVA and VX-152 300mg for Cohort 2B.

The adjusted means and 95% CI of the treatment effect for each triple combination at Day 15 in Cohort 2A and through Day 29 in Cohort 2B, with a 1-sided *P* value, will be estimated for all within-treatment and between-treatment comparisons. Contrasts based on the fixed effects in the model, defined at the baseline covariate mean for the combined treatment groups using unique subjects in the FAS who have at least one post-baseline measurement through Day 15 for Cohort 2A and through Day 29 for Cohort 2B, will be used to estimate the treatment effect at Day 15 in Cohort 2A and the average treatment effect through Day 29 (Day 15 and Day 29 only) in Part 2 Cohort 2B, with the corresponding 1-sided *P* value for the 1-sided hypothesis test.

In addition, descriptive analyses of the change from baseline will be performed for all treatment groups by post-baseline visit.

The adjusted mean (with 95% CI) obtained from the MMRM analysis at each post-baseline visit will also be plotted separately for each cohort. In addition, a waterfall plot showing subject-level absolute change in $ppFEV_1$ at Day 15 for Cohort 2A and at Day 29 for Cohort 2B will be presented, by treatment group.

[redacted]

[redacted]

8.3.2 Analysis of Secondary Efficacy Variables

The secondary efficacy variables include:

- Relative change in $ppFEV_1$ from baseline at Day 15 (Part 1 and Part 2 Cohort 2A) and through Day 29 (Part 2 Cohort 2B)
- Absolute change in the CFQ-R respiratory domain score from baseline at Day 15 (Part 1 and Part 2 Cohort 2A) and at Day 29 (Part 2 Cohort 2B)

8.3.2.1 Relative change in ppFEV1 from baseline at Day 15 (Part 1 and Part 2 Cohort 2A) and through Day 29 (Part 2 Cohort 2B)

The relative change in $ppFEV_1$ from baseline is defined in Section 8.1. Analysis of this variable will be based on an MMRM model, similar to the primary analysis of the primary efficacy variable. The presentation of results will also be similar.

8.3.2.2 Absolute change in the CFQ-R respiratory domain score from baseline at Day 15 (Part 1 and Part 2 Cohort 2A) and at Day 29 (Part 2 Cohort 2B)

The absolute change in the CFQ-R respiratory domain score from baseline at Day 15 (Part 1 and Part 2 Cohort 2A) and at Day 29 (Part 2 Cohort 2B) will use the 'Adolescents and Adults' Version for ages 14 and above at baseline, and will be based on the *CFQ-R scaled scores*, [redacted] For Part 1, the analysis of this variable will be based on an ANCOVA model with treatment as a fixed effect. For Part 2, the analysis of this variable will be based on an MMRM model, similar to the analysis of the primary efficacy variable. The continuous baseline CFQ-R respiratory domain score will be used as a covariate in Parts 1 and 2. The presentation of results will also be similar.

[redacted]

[redacted]

[redacted]

8.4 Pharmacodynamic Analysis

The sweat chloride measurement for a given visit will be calculated as the mean of the non-missing sweat chloride measurements obtained on the left and right arms at that visit. If one of the two arm measurements at a time point is missing, the other will be used as the mean. A volume ≥15 μL is required for an accurate determination of sweat chloride. Any results reported as having volume <15 μL will be considered missing. Any sweat chloride values reported as <10 mmol/L or >160 mmol/L will be considered missing.

The analysis of the pharmacodynamic (PD) effect of VX-152 in TC with VX-661/IVA (all parts) on sweat chloride concentrations will be described in this section.

8.4.1.1 Primary Analysis of the Dose Response trend of absolute change in sweat chloride from baseline at Day 15 in Part 1

The null hypothesis to be tested is that the dose response of the mean absolute change from baseline at Day 15 for sweat chloride is not decreasing between placebo and the TC dose groups. The test will be performed using the MCP procedure with the pre-specified contrasts provided in Section 6.2.2.1, within a linear MMRM framework using PROC GLIMMIX in SAS. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects, with continuous baseline sweat chloride as a covariate. The dose response test will be based on the 1-sided maximum *t*-statistic of the individual *t*-statistics for the multiple pre-specified contrasts at alpha = 5%, based on the treatment group means at Day 15, using a compound symmetry covariance structure for the within-subject errors

The presentation of results for the treatment effect at Day 15, and the treatment effect by visit will be similar to the primary analysis of the primary efficacy variable. The corresponding *P* value for the decreasing dose response trend will be provided. In addition, descriptive analyses of the change from baseline will be performed for all treatment groups at each post-baseline visit. A waterfall plot showing the subject-level absolute change from baseline in sweat chloride at Day 15 will be presented, by treatment group.

8.4.1.2 Absolute change in sweat chloride from baseline at Day 15 (Part 2 Cohort 2A) and through Day 29 (Part 2 Cohort 2B)

The analysis of the absolute change in sweat chloride from baseline at Day 15 (Part 2 Cohort 2A) and through Day 29 (Part 2 Cohort 2B) using the average of Day 15 and Day 29, will be based on an MMRM model fitted to each cohort, separately, similar to the analysis of the primary efficacy variable, with the continuous baseline sweat chloride as a covariate. The presentation of results will also be similar.

The adjusted mean (with 95% CI) obtained from the MMRM analysis at each post-baseline visit in the Treatment Period will also be plotted by treatment group, for each cohort, separately.

In addition, descriptive analyses of the change from baseline will be performed for all treatment groups at each post-baseline visit.

A waterfall plot showing the subject-level absolute change in sweat chloride at Day 15 and Day 29, as applicable, will be presented, by treatment group.

[redacted]

8.5 Safety Analysis

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

- Adverse events
- Clinical laboratory values (hematology, chemistry, coagulation, and urinalysis)
- Standard 12-lead electrocardiograms
- Vital signs
- Pulse oximetry

Safety endpoints will be analyzed based on the Safety Set. Only a descriptive analysis of safety will be performed. Safety results for treatment groups in Part 2 Cohort 2A and Part 2 Cohort 2B will be presented separately, and overall.

For Part 2, the Safety Set refers to the Safety Set for the Treatment Period.

8.5.1 Adverse Events

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

For Part 1:

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

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

For Part 2:

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

TEAE during the Run-in Period: 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 the Run-in Period

TEAE during the Treatment Period: 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 the Treatment Period

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

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, the AEs will be classified as TEAEs.

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

An adverse event overview table will be provided for the TE period (TE period for the Treatment Period for Part 2) by treatment group, 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 Treatment Discontinuation
- Subjects with TEAEs Leading to Drug Interruption
- 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 for all applicable periods, and post-treatment AEs, will be presented in an individual subject data listing based on the All Subjects Set. Subjects who enrolled from Study 661-110 will be identified in the listing based on the subject ID.

8.5.2 Clinical Laboratory

For the treatment-emergent laboratory assessments, the observed values and change from baseline values of the continuous hematology, chemistry, and coagulation results will be summarized in SI units at each scheduled visit, by treatment group and part.

The number and percentage of subjects meeting at least 1 threshold analysis criterion event during the TE period, or accordingly, the TE period for the Treatment Period in Part 2, will be summarized by treatment group and overall for each part. The threshold analysis criterion shift from baseline will also be summarized for selected laboratory parameters. The threshold analysis criteria are provided in Appendix H.

For select LFT laboratory test (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin), a scatter plot of the maximum treatment-emergent value versus the 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, for each part.

Results of abnormal urinalysis and positive urine/serum pregnancy test will be listed in individual subject data listings only.

In addition, a listing containing individual subject hematology, chemistry, urinalysis, and coagulation values outside the normal reference ranges will be provided. This listing will include data from both scheduled and unscheduled visits.

8.5.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided at each scheduled visit and time point, by treatment group, for each part, for the following ECG interval measurements (in ms): RR, PR, QT, and QT corrected for HR (QTcF), QRS duration, and HR (beats per minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE period, or accordingly, the TE period for the Treatment Period in Part 2, will be summarized by treatment group and overall, for each part. The threshold analysis criteria are provided in Appendix H.

8.5.4 Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized by treatment group, at each scheduled visit, for each part and cohort, as applicable. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (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, or TE period for the Treatment Period in Part 2, will be summarized by treatment group and overall, for each part. The threshold analysis criteria are provided in Appendix H.

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

8.5.5 Pulse Oximetry

For the treatment-emergent pulse oximetry measurements, a summary of observed values and change from baseline values will be provided at each scheduled visit, for the percent of oxygen saturation, by treatment group, for each part.

The number and percentage of subjects with shift changes from baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the TE Period, or accordingly, the TE period for the Treatment Period in Part 2, will be summarized by treatment group and overall, for each part.

8.5.6 Physical Examination

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

8.5.7 Other Safety Analysis

Not applicable.

9 Interim and IDMC Analysis

9.1 Interim Analysis

Interim analyses may be performed for each cohort after 50% or 100% of subjects in the cohort have completed the Day 15 or Day 29 Visit. The results of these analyses will be reviewed by a limited Vertex team. When an interim analysis is performed after all subjects in 1 part have completed the Safety Follow-up Visit, results from that part will be unblinded for full review by the Vertex study team.

9.1.1 Summary of the Flow of Data for Interim Analyses by a Limited Vertex Team

To protect the integrity of the treatment assignment and study data, the following steps for the flow of data will be executed for interim analysis:

1. The Vertex Biometrics group will prepare the SAS codes, SDTM/ADaM data sets, and blinded outputs (tables, figures and listings) using dummy treatment codes, dummy spirometry data, and dummy sweat chloride data;
2. The IWRS vendor, [redacted] will provide the unblinded treatment codes to an independent unblinded Vertex Biometrics group [redacted]
3. Biomedical Systems (BMS) will provide the unblinded spirometry data directly to an independent unblinded Vertex Biometrics group [redacted] will provide the unblinded sweat chloride data directly to an independent unblinded Vertex Biometrics group [redacted]

4. The independent unblinded Vertex Biometrics group that is not involved with the conduct of the study will generate the unblinded outputs and provide them directly to the limited Vertex team for their review.

9.2 IDMC Analysis

An independent data monitoring committee (IDMC) was formed before study initiation. The IDMC's objectives and operational details were defined in a separate document (IDMC Charter) which was finalized before the first subject was screened in the study. The IDMC's planned safety reviews of study data are outlined in the IDMC Charter and IDMC Statistical Analysis Plan. Further, planned ongoing reviews of key study data by the limited Vertex team are also described in the IDMC Statistical Analysis Plan.

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.

11 LIST OF APPENDICES

Appendix A: Schedule of Assessments

Table 11-1 Study VX16-152-102: Schedule of Assessments for Part 1

Event/Assessment[a]	Screening	Treatment Period[b]					ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose
	Days -28 to -1[d]	Day 1	Days 3 and 5[e] (or Days 4/6 or Days 3/6)[f]	Day 8 (± 1 day)	Day 11[e] (± 1 day)	Day 15 (± 1 day)		
Informed consent	X							
Randomization[g]		X						
Demographics	X							
Medical history	X							
Ophthalmological history	X							
CFQ-R[h,i]		X				X	X[j]	X

[a] Assessments will be performed in the order presented, unless noted otherwise. All assessments will be performed before dosing, unless noted otherwise. Assessments that are collected before and after dosing will only be collected once if study drug is not administered on the day of the visit (i.e., premature discontinuation of study drug treatment).

[b] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 8.1.3.

[c] If the subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the decision to terminate study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

[d] All screening results must be reviewed before randomization, unless noted otherwise.

[e] Days 3, 5, and 11 assessments may be collected at the clinic, at a local laboratory, or during a visit by a qualified individual (e.g., home nurse).

[f] Day 3 and Day 5 assessments will be performed at least 2 days apart, with the first day of assessments occurring no earlier than Day 3 and the second day of assessments occurring no later than Day 6. (i.e., Assessments will be performed on Days 3 and 5, Days 4 and 6, or Days 3 and 6.)

[g] Randomization may occur on the previous day (Day -1) after all inclusion and exclusion criteria have been confirmed. See Section 8.1.3.

[h] CFQ-R must be completed before the start of any other assessments scheduled at that visit.

[i] The predose assessment on Day 1 may be performed on the previous day (Day -1) if randomization has occurred.

Table 11-1 Study VX16-152-102: Schedule of Assessments for Part 1

Event/Assessment[a]	Screening	Treatment Period[b]					ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose
	Days -28 to -1[d]	Day 1	Days 3 and 5[e] (or Days 4/6 or Days 3/6)[f]	Day 8 (± 1 day)	Day 11[e] (± 1 day)	Day 15 (± 1 day)		
Weight[k]	X	X		X		X	X	X
Height[k]	X							
Vital signs[l]	X	X		X		X	X	X
Pulse oximetry[l]	X	X		X		X	X	X
Physical examination[m]	Complete	Abbreviated		Abbreviated		Abbreviated	Abbreviated	Complete
Ophthalmologic examination[n]	X							
Standard 12-lead ECG[o]	X	X		X		X	X	X
Sweat chloride[i,p]	X	X		X		X	X	X
Spirometry[q]	X	X		X		X	X	X

[j] Subjects will complete the CFQ-R at the ETT Visit only if it has been 2 weeks or more since their last visit.

[k] Weight and height will be measured with shoes off.

[l] Vital signs and pulse oximetry will be collected after the subject has been seated for at least 5 minutes.

[m] Complete and abbreviated PEs are described in Section 11.7.3. Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator or healthcare provider.

[n] The ophthalmological examination can be performed at any time during the Screening Period through the Day 1 Visit (before the first dose of study drug). The screening ophthalmological examination does not have to be performed if there is documentation of an examination that met protocol criteria and was within 3 months before the date of informed consent, or if there is documentation of bilateral lens removal for the subject.

[o] All standard 12-lead ECGs will be performed after the subject has been seated for at least 5 minutes. ECGs will be collected before procedures that may affect heart rate (e.g., blood sampling). On Days 1 and 15, ECGs will be collected before dosing and 4 hours (± 1 hour) after dosing. At all other visits, ECGs will be collected before dosing (as applicable). ECGs collected on Day 1 before dosing will be performed in triplicate.

[p] Sweat chloride will be measured in all subjects. If the value cannot be determined from the screening test, a sweat chloride value documented in the subject's medical record may be used to establish eligibility.

[q] Spirometry may be performed pre- or post-bronchodilator at the Screening Visit. Spirometry will be performed pre-bronchodilator, before the morning dose of study drugs, and should be performed at approximately the same time at every other study visit. On Days 1 and 15, spirometry will also be performed pre-bronchodilator 5 hours (± 1 hour) after study drug administration.

Table 11-1 Study VX16-152-102: Schedule of Assessments for Part 1

Event/Assessment[a]	Screening	Treatment Period[b]					ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose
	Days -28 to -1[d]	Day 1	Days 3 and 5[e] (or Days 4/6 or Days 3/6)[f]	Day 8 (± 1 day)	Day 11[e] (± 1 day)	Day 15 (± 1 day)		
Urinalysis[i]	X	X		X		X	X	X
Pregnancy test (all females of childbearing potential)	Serum	Urine					Serum	Serum
CFTR genotype[r]	X							

[r] *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility.

Table 11-1 Study VX16-152-102: Schedule of Assessments for Part 1

Event/Assessment[a]	Screening	Treatment Period[b]					ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose
	Days -28 to -1[d]	Day 1	Days 3 and 5[e] (or Days 4/6 or Days 3/6)[f]	Day 8 (± 1 day)	Day 11[e] (± 1 day)	Day 15 (± 1 day)		
FSH[s]	X							
G6PD activity test[t]	X							
[redacted]								
Serum chemistry and hematology[i]	X	X	X[e,v]	X	X[e,v]	X	X	X
Coagulation[i]	X	X		X		X		X
PK sampling[w]		X		X		X	X	
Study drug dosing[x]		Day 1 through Day 15						
AEs, medications[y], treatments, and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit							

s FSH will be measured for any suspected postmenopausal female subjects with at least 12 months of continuous spontaneous amenorrhea.

t A single blood sample will be collected for the G6PD activity test.

[redacted]

v On Days 3, 5, and 11, the following parameters will be measured: lactate dehydrogenase, total and direct bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase.

w Blood samples will be collected for PK analysis of VX-152, VX-661, M1-661, IVA, and M1-IVA. On Day 1, samples will be collected before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to the morning dose). On Day 8, a predose sample will be collected before the morning dose of study drug (0 hours). On Day 15, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing. At the ETT Visits, a single blood sample for PK analysis will be collected.

x The last dose of study drug will be the morning dose on Day 15.

y Refer to Section 9.4 for details.

Table 11-2 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2A

Event/Assessment[a]	Screening	Run-in Period		Treatment Period[b]					Washout Period	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose[d]
	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]	Day 8 (± 1 day)	Day 11[g] (± 1 day)	Day 15 (± 1 day)	Day 29 (± 3 days)		
Informed consent	X										
Randomization[i]				X							
Demographics	X										
Medical history	X										
Ophthalmological history	X										
CFQ-R[j,k]				X		X		X	X	X[l]	X

[a] Assessments will be performed in the order presented, unless noted otherwise. All assessments will be performed before dosing, unless noted otherwise. Assessments that are collected before and after dosing will only be collected once if study drug is not administered on the day of the visit (i.e., premature discontinuation of study drug treatment).

[b] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 8.1.3.

[c] If the subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the decision to terminate study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

[d] Subjects who meet criteria specified in Section 8.1.5 will not have a Safety Follow-up Visit.

[e] All screening results must be reviewed before the subject receives VX-661/IVA in the Run-in Period on Day -28, unless noted otherwise.

[f] The Day -14 Visit is only required for subjects who are naïve to VX-661/IVA treatment.

[g] Days 3, 5, and 11 assessments may be collected at the clinic, at a local laboratory, or during a visit by a qualified individual (e.g., home nurse).

[h] Day 3 and Day 5 assessments will be performed at least 2 days apart, with the first day of assessments occurring no earlier than Day 3 and the second day of assessments occurring no later than Day 6. (i.e., Assessments will be performed on Days 3 and 5, Days 4 and 6, or Days 3 and 6.)

[i] Randomization may occur on the previous day (Day -1) after all inclusion and exclusion criteria and criteria for entry into the Treatment Period have been confirmed. See Section 8.1.3.

[j] CFQ-R must be completed before the start of any other assessments scheduled at that visit.

[k] The predose assessment on Day 1 may be performed on the previous day (Day -1) if randomization has occurred.

[l] Subjects will complete the CFQ-R at the ETT Visit only if it has been 2 weeks or more since their last visit.

Table 11-2 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2A

	Screening	Run-in Period		Treatment Period[b]					Washout Period		Safety Follow-up 28 (± 7) Days After Last Dose[d]
Event/Assessment[a]	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]	Day 8 (± 1 day)	Day 11[g] (± 1 day)	Day 15 (± 1 day)	Day 29 (± 3 days)	ETT Visit[c]	
Weight[m]	X	X		X		X		X	X	X	X
Height[m]	X										
Vital signs[n]	X	X		X		X		X	X	X	X
Pulse oximetry[n]	X	X		X		X		X	X	X	X
Physical examination[o]	Complete	Abbrev-iated		Abbreviated		Abbreviated		Abbreviated	Abbreviated	Abbreviated	Complete
Ophthalmologic examination[p]	X										
Standard 12-lead ECG[q]	X	X		X		X		X	X	X	X
Sweat chloride[k,r]	X		X	X		X		X	X	X	
Spirometry[s]	X		X	X		X		X	X	X	X

[m] Weight and height will be measured with shoes off.

[n] Vital signs and pulse oximetry will be collected after the subject has been seated for at least 5 minutes.

[o] Complete and abbreviated PEs are described in Section 11.7.3. Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator or healthcare provider.

[p] The ophthalmological examination can be performed at any time during the Screening Period through the Day 1 Visit (before the first dose of study drug). The screening ophthalmological examination does not have to be performed if there is documentation of an examination that met protocol criteria and was within 3 months before the date of informed consent, or if there is documentation of bilateral lens removal for the subject.

[q] All standard 12-lead ECGs will be performed after the subject has been seated for at least 5 minutes. ECGs will be collected before procedures that may affect heart rate (e.g., blood sampling). On Days 1 and 15, ECGs will be collected before dosing and 4 hours (± 1 hour) after dosing. At all other visits, ECGs will be collected before dosing (as applicable). ECGs collected on Day 1 before dosing will be performed in triplicate.

[r] Sweat chloride will be measured in all subjects. If the value cannot be determined from the screening test, a sweat chloride value documented in the subject's medical record may be used to establish eligibility.

[s] Spirometry may be performed pre- or post-bronchodilator at the Screening Visit. Spirometry will be performed pre-bronchodilator, before the morning dose of study drugs, and should be performed at approximately the same time at every other study visit. On Days 1 and 15, spirometry will also be performed pre-bronchodilator 5 hours (± 1 hour) after study drug administration.

Table 11-2 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2A

Event/Assessment[a]	Screening	Run-in Period		Treatment Period[b]					Washout Period	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose[d]
	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]	Day 8 (± 1 day)	Day 11[g] (± 1 day)	Day 15 (± 1 day)	Day 29 (± 3 days)		
Urinalysis[k]	X	X		X		X		X	X	X	X
Pregnancy test (all females of childbearing potential)	Serum	Urine		Urine				Urine		Serum	Serum
CFTR genotype[t]	X										
FSH[u]	X										
G6PD activity test[v]	X										
[redacted]											
Serum chemistry and hematology[k]	X	X		X	X[g,x]	X	X[g,x]	X	X	X	X
Coagulation[k]	X	X		X		X		X			X
PK sampling[y]				X		X		X		X[y]	
VX-661/IVA dosing[z]		Day -28 through Day 29									

t *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before Day -28, a previous *CFTR* genotype laboratory report may be used to establish eligibility.

u FSH will be measured for any suspected postmenopausal female subjects with at least 12 months of continuous spontaneous amenorrhea.

v A single blood sample will be collected for the G6PD activity test.

[redacted]

x On Days 3, 5, and 11, the following parameters will be measured: lactate dehydrogenase, total and direct bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase.

y Blood samples will be collected for PK analysis of VX-152, VX-661, M1-661, IVA, and M1-IVA. On Day 1, samples will be collected before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to morning dose). On Day 8, a predose sample will be collected before the morning dose of study drug (0 hours). On Day 15, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing. At ETT Visits, a single blood sample for PK analysis will only be collected from subjects who discontinued study drug after Day 1, but before Day 15 PK was collected.

Table 11-2 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2A

Event/Assessment[a]	Screening	Run-in Period		Treatment Period[b]					Washout Period	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose[d]
	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]	Day 8 (± 1 day)	Day 11[g] (± 1 day)	Day 15 (± 1 day)	Day 29 (± 3 days)		
VX-152 or placebo dosing[aa]				Day 1 through Day 15							
AEs, medications[bb], treatments and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit										

z The last dose of VX-661/IVA will be the morning dose on Day 29.
aa The last dose of VX-152 or placebo will be the morning dose on Day 15.
bb Refer to Section 9.4 for details.

Table 11-3 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2B

	Screening	Run-in Period		Treatment Period[b]					Washout Period		Safety Follow-up 28 (± 7) Days After Last Dose[d]
Event/Assessment[a]	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]	Day 8 (± 1 day)	Day 11[g] (± 1 day)	Day 15 and Day 29 (± 1 day)	Day 43 (± 3 days)	ETT Visit[c]	
Informed consent	X										
Randomization[i]				X							
Demographics	X										
Medical history	X										
Ophthalmological history	X										
CFQ-R[j,k]				X		X		X	X	X[l]	X

[a] Assessments will be performed in the order presented, unless noted otherwise. All assessments will be performed before dosing, unless noted otherwise. Assessments that are collected before and after dosing will only be collected once if study drug is not administered on the day of the visit (i.e., premature discontinuation of study drug treatment).

[b] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 8.1.3.

[c] If the subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the decision to terminate study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

[d] Subjects who meet criteria specified in Section 8.1.5 will not have a Safety Follow-up Visit.

[e] All screening results must be reviewed before the subject receives VX-661/IVA in the Run-in Period on Day -28, unless noted otherwise.

[f] The Day -14 Visit is only required for subjects who are naïve to VX-661/IVA treatment.

[g] Days 3, 5, and 11 assessments may be collected at the clinic, at a local laboratory, or during a visit by a qualified individual (e.g., home nurse).

[h] Day 3 and Day 5 assessments will be performed at least 2 days apart, with the first day of assessments occurring no earlier than Day 3 and the second day of assessments occurring no later than Day 6. (i.e., Assessments will be performed on Days 3 and 5, Days 4 and 6, or Days 3 and 6.)

[i] Randomization may occur on the previous day (Day -1) after all inclusion and exclusion criteria and criteria for entry into the Treatment Period have been confirmed. See Section 8.1.3.

[j] CFQ-R must be completed before the start of any other assessments scheduled at that visit.

[k] The predose assessment on Day 1 may be performed on the previous day (Day -1) if randomization has occurred.

Table 11-3 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2B

Event/Assessment[a]	Screening	Run-in Period		Treatment Period[b]					Washout Period	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose[d]
	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]	Day 8 (± 1 day)	Day 11[g] (± 1 day)	Day 15 and Day 29 (± 1 day)	Day 43 (± 3 days)		
Weight[m]	X	X		X		X		X	X	X	X
Height[m]	X										
Vital signs[n]	X	X		X		X		X	X	X	X
Pulse oximetry[n]	X	X		X		X		X	X	X	X
Physical examination[o]	Complete	Abbrev-iated		Abbrev-iated		Abbrev-iated		Abbrev-iated	Abbreviated	Abbreviated	Complete
Ophthalmologic examination[p]	X										
Standard 12-lead ECG[q]	X	X		X		X		X	X	X	X
Sweat chloride[k,r]	X		X	X		X		X	X	X	
Spirometry[s]	X		X	X		X		X	X	X	X

[l] Subjects will complete the CFQ-R at the ETT Visit only if it has been 2 weeks or more since their last visit.

[m] Weight and height will be measured with shoes off.

[n] Vital signs and pulse oximetry will be collected after the subject has been seated for at least 5 minutes.

[o] Complete and abbreviated PEs are described in Section 11.7.3. Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator or healthcare provider.

[p] The ophthalmological examination can be performed at any time during the Screening Period through the Day 1 Visit (before the first dose of study drug). The screening ophthalmological examination does not have to be performed if there is documentation of an examination that met protocol criteria and was within 3 months before the date of informed consent, or if there is documentation of bilateral lens removal for the subject.

[q] Standard 12-lead ECGs will be performed after the subject has been seated for at least 5 minutes. ECGs will be collected before procedures that may affect heart rate (e.g., blood sampling). On Days 1, 15, and 29, ECGs will be collected before dosing and 4 hours (± 1 hour) after dosing. At all other visits, ECGs will be collected before dosing (as applicable). ECGs collected on Day 1 before dosing will be performed in triplicate.

[r] Sweat chloride will be measured in all subjects. If the value cannot be determined from the screening test, a sweat chloride value documented in the subject's medical record may be used to establish eligibility.

Table 11-3 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2B

Event/Assessment[a]	Screening	Run-in Period		Treatment Period[b]					Washout Period	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose[d]
	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]	Day 8 (± 1 day)	Day 11[g] (± 1 day)	Day 15 and Day 29 (± 1 day)	Day 43 (± 3 days)		
Urinalysis[k]	X	X		X		X		X	X	X	X
Pregnancy test (all females of childbearing potential)	Serum	Urine		Urine				Urine		Serum	Serum
CFTR genotype[t]	X										
FSH[u]	X										
G6PD activity test[v]	X										
[redacted]											
Serum chemistry and hematology[k]	X	X		X	X[g,x]	X	X[g,x]	X	X	X	X
Coagulation[k]	X	X		X		X		X			X
PK sampling[y]				X		X		X		X[y]	

[s] Spirometry may be performed pre- or post-bronchodilator at the Screening Visit. Spirometry will be performed pre-bronchodilator, before the morning dose of study drugs, and should be performed at approximately the same time at every other study visit. On Days 1, 15, and 29, spirometry will be performed pre-bronchodilator 5 hours (± 1 hour) after study drug administration.

[t] *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before Day -28, a previous *CFTR* genotype laboratory report may be used to establish eligibility.

[u] FSH will be measured for any suspected postmenopausal female subjects with at least 12 months of continuous spontaneous amenorrhea.

[v] A single blood sample will be collected for the G6PD activity test.

[redacted]

[x] On Days 3, 5, and 11, the following parameters will be measured: lactate dehydrogenase, total and direct bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase.

[y] Blood samples will be collected for PK analysis of VX-152, VX-661, M1-661, IVA, and M1-IVA. On Day 1, samples will be collected before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to morning dose). On Day 8, a predose sample will be collected before the morning dose of study

Table 11-3 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2B

Event/Assessment[a]	Screening	Run-in Period		Treatment Period[b]					Washout Period	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose[d]
	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]	Day 8 (± 1 day)	Day 11[g] (± 1 day)	Day 15 and Day 29 (± 1 day)	Day 43 (± 3 days)		
VX-661/IVA dosing[z]		Day -28 through Day 43									
VX-152 or placebo dosing[aa]				Day 1 through Day 29							
AEs, medications[bb], treatments and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit										

drug (0 hours). On Day 15, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing. On Day 29, a sample will be collected before the morning dose (0 hours). At ETT Visits, a single blood sample for PK analysis will only be collected from subjects who discontinued study drug after Day 1, but before Day 29.

[z] The last dose of VX-661/IVA will be the morning dose on Day 43.

[aa] The last dose of VX-152 or placebo will be the morning dose on Day 29.

[bb] Refer to Section 9.4 for details.

Appendix B: Analysis Visit Windows for Safety and Efficacy Assessments

Table 11-3 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)
Safety Assessment (Part 1)			
Serum Chemistry I (lactate dehydrogenase, total and direct bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase)	Day 1 (Baseline) Day 3 Day 5 Day 8 Day 11 Day 15 Safety Follow-up	1 3 5 8 11 15 43	≤1 [1, 4] (4, 6] (6, 9] (9, 13] (13, 29] Use nominal visit
Serum Chemistry II (all others) Hematology Coagulation Vital Signs (including Weight) Urinalysis (nominal visit for all visits)	Day 1 (Baseline) Day 8 Day 15 Safety Follow-up	1 8 15 43	≤1 [1, 12] (12, 29] Use nominal visit
Standard 12-Lead ECG	Day 1 (Baseline; before dosing) Day 1 (4 hours after dosing) Day 8 Day 15 (before dosing and 4 hours after dosing) Safety Follow-up	1 1 8 15 43	Use nominal visit for all visits
Safety Assessment (Part 2 Cohort 2A)			
Serum Chemistry I (lactate dehydrogenase, total and direct bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase)	Day 1 (Baseline) Day 3 Day 5 Day 8 Day 11 Day 15 Day 29 Safety Follow-up	1 3 5 8 11 15 29 57	≤1 [1, 4] (4, 6] (6, 9] (9, 13] (13, 22] (22, 43] Use nominal visit

[a] Visit name is used to report data in tables, listings and figures.
[b] Target day time point per protocol is predose, except for ECG measurements.

Table 11-3 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)
Serum Chemistry II (all others) Hematology Vital Signs (including Weight) Urinalysis (nominal visit for all visits)	Day 1 (Baseline) Day 8 Day 15 Day 29 Safety Follow-up	1 8 15 29 57	≤1 [1, 12] (12, 22] (22, 43] Use nominal visit
Coagulation	Day 1 (Baseline) Day 8 Day 15 Safety Follow-up	1 8 15 57	≤1 [1, 12] (12, 36] Use nominal visit
Standard 12-Lead ECG	Day 1 (Baseline; before dosing) Day 1 (4 hours after dosing) Day 8 Day 15 (before dosing and 4 hours after dosing) Day 29 Safety Follow-up	1 1 8 15 29 57	Use nominal visit for all visits
Safety Assessment (Part 2 Cohort 2B)			
Serum Chemistry I (lactate dehydrogenase, total and direct bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase)	Day 1 (Baseline) Day 3 Day 5 Day 8 Day 11 Day 15 Day 29 Day 43 Safety Follow-up	1 3 5 8 11 15 29 43 71	≤1 [1, 4] (4, 6] (6, 9] (9, 13] (13, 22] (22, 36] (36, 57] Use nominal visit
Serum Chemistry II (all others) Hematology Vital Signs (including Weight) Urinalysis (nominal visit for all visits)	Day 1 (Baseline) Day 8 Day 15 Day 29 Day 43 Safety Follow-up	1 8 15 29 43 71	≤1 [1, 12] (12, 22] (22, 36] (36, 57] Use nominal visit

Table 11-3 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)
Coagulation	Day 1 (Baseline) Day 8 Day 15 Day 29 Safety Follow-up	1 8 15 29 71	≤1 [1, 12] (12, 22] (22, 50] Use nominal visit
Standard 12-Lead ECG	Day 1 (Baseline; before dosing) Day 1 (4 hours after dosing) Day 8 Day 15 (before dosing and 4 hours after dosing) Day 29 Safety Follow-up	1 1 8 15 29 71	Use nominal visit for all visits
Efficacy Assessment (Part 1)			
Spirometry	Day 1 (Baseline; predose) Day 8 Day 15 (predose) Safety Follow-up	1 8 15 43	≤1 (1, 12] (12, 29] Use nominal visit
Sweat Chloride	Day 1 Day 8 Day 15 Safety Follow-up	1 8 15 43	≤1 (1, 12] (12, 29] Use nominal visit
CFQ-R	Day 1 Day 15 Safety Follow-up	1 15 43	≤1 (1, 29] Use nominal visit
Efficacy Assessment (Part 2 Cohort 2A)			
Spirometry	Day 1 (Baseline; pedose) Day 8 Day 15 (predose Day 29 Safety Follow-up	1 8 15 29 57	≤1 (1, 12] (12, 22] (22, 43] Use nominal visit

Table 11-3 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)
Sweat Chloride CFQ-R	Day 1 Day 8 Day 15 Day 29 Safety Follow-up	1 8 15 29 57	≤1 (1, 12] (12, 22] (22, 43] Use nominal visit
Efficacy Assessment (Cohort 2B)			
Spirometry	Day 1 (Baseline; predose) Day 8 Day 15 (before dosing and 5 hours after dosing) Day 29 Day 43 Safety Follow-up	1 8 15 29 43 71	≤1 (1, 12] (12, 22] (22, 36] (36, 57] Use nominal visit
Sweat Chloride CFQ-R	Day 1 Day 8 Day 15 Day 29 Day 43 Safety Follow-up	1 8 15 29 43 71	≤1 (1, 12] (12, 22] (22, 36] (36, 57] Use nominal visit

Notes:
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.

Table 11-3 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)
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) 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 (excluding PK dosing dates). When a subject is lost to follow up without ETT, impute the last dose date as the last on-treatment visit date. 4. Missing Date for Drug Interruption If the dates for drug interruption are completely missing or partially missing and cannot determine which period the interruption occurred, then assume the interruption occurred during the treatment period for 1 day.			

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 or post categorization of a medication is described below.

Table 11-4 Prior, Concomitant, and Post Categorization of a Medication in Part 1

	Medication Stop Date		
Medication Start Date	**< First Dose Date of Study Drug**	**≥ First Dose Date and ≤ End Date of TE Period**	**> End Date of TE Period**
< First dose date of study drug	P	PC	PCA
≥ First dose date and ≤ End date of TE period	-	C	CA
> End date of TE period	-	-	A

P: Prior; C: Concomitant; A: Post

Table 11-5 Prior, Concomitant, and Post Categorization of a Medication in Part 2

	Medication Stop Date			
Medication Start Date	**< First Dose Date of Run-in TE Period**	**≥ First Dose Date and ≤ End Date of Run-in TE Period**	**≥ First Dose Date and ≤ End Date of Treatment TE Period**	**> End Date of Treatment TE Period**
< First dose date of Run-in TE period	P	PC1	PC1C2	PC1C2A
≥ First dose date and ≤ End date of Run-in TE Period	-	C1	C1C2	C1C2A
≥ First dose date and ≤ End date of Treatment TE Period	-	-	C2	C2A
> End date of Treatment TE Period	-	-	-	A

P: Prior; C1: Concomitant during the Run-in Period; C2: Concomitant during the Treatment Period; A: Post

Appendix D: Important Protocol Deviation Programming Rules

Important protocol deviations before first dose

1. Inclusion criteria:
   a) I1: Subject will sign and date an informed consent form (ICF).
   b) I3: Subjects will be aged 18 years or older on the date of informed consent.
   c) I4: Body weight ≥35 kg.
   d) I6: Subjects must have an eligible CFTR genotype as noted below. If the screening CFTR genotype result is not received before randomization (Part 1) or before Day 28 (Part 2), a previous CFTR genotype laboratory report may be used to establish eligibility. Note: Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.5).

      Part 1: Heterozygous for F508del with a second CFTR allele carrying an MF mutation that is not likely to respond to VX-661 and/or IVA therapy (Appendix A)

      Part 2: Homozygous for F508del
   e) I7: Subjects must have an FEV1 ≥40% and ≤90% of predicted normal for age, sex, and height (equations of the Global Lung Function Initiative [GLI])9 at the Screening Visit. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria6 for acceptability and repeatability.
2. Exclusion criteria:
   a) E4: History of hemolysis.
   b) E5: G6PD deficiency, defined as G6PD activity less than the lower limit of normal (LLN) or 70% of the mean of the LLN and the ULN, whichever is greater.
   c) E6: Any of the following abnormal laboratory values at screening:
      - Hemoglobin <10 g/dL
      - Total bilirubin ≥2 × ULN
      - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN
      - Abnormal renal function defined as glomerular filtration rate ≤50 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease Study Equation)for subjects ≥18 years of age

d) E10: A standard digital ECG demonstrating QTc >450 msec at screening. If QTc exceeds 450 msec for the screening ECG, the ECG should be repeated 2 more times during the Screening Period, and the subject will be excluded if the average of the 3 QTc values is >450 msec.

e) E16: Use of restricted medications as defined in the clinical study protocol, within the specified window before the first dose of study drug (Day 1 in Part 1, Day -28 in Part 2).

f) E17: Pregnant or nursing females: Females of childbearing potential must have a negative pregnancy test at screening and Day 1.

Important protocol deviations during the Treatment Period

1. Compliance < 80% based on percentage of tablets taken
2. Use of prohibited medications
3. Actual treatment received is different from the randomized treatment

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 G: Imputation Rules for Missing AE dates

G.1 Part 1

Imputation rules for missing or partial AE start date for Part 1 are defined below.

- **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.

G.2 Part 2

Imputation rules for missing or partial AE start date for Part 2 are defined below.

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

Imputation rules for partial AE end date are defined below:

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 H: Criteria for Threshold Analysis

Table 11-10 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Clinical Chemistry (LFT)		
ALT	>ULN - ≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >8x - ≤ 20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
AST	>ULN - ≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >8x - ≤ 20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
ALT or AST	(ALT>ULN - ≤ 3xULN) or (AST>ULN - ≤ 3xULN) (ALT>3x - ≤ 5xULN) or (AST>3x - ≤ 5xULN) (ALT>5x- ≤ 8xULN) or (AST>5x - ≤ 8xULN) (ALT>8x - ≤ 20xULN) or (AST>8x - ≤ 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 11-10 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)		
Albumin	<LLN - ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>1x - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Creatinine	>ULN - ≤ 1.5xULN >1.5 - ≤ 3.0xULN >3.0 - ≤ 6.0xULN >6.0xULN	CTCAE grades 1-4
Lipase	>ULN - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
Hematology		
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
	Platelet increased >ULN	No CTCAE available
Reticulocytes	<LLN >ULN	No CTCAE

Table 11-11 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
HR	Bradycardia	Per HV grade 2, 3, plus shift change
	<50 bpm	
	<45 bpm	
	Decrease from baseline ≥10 bpm	
	Decrease from baseline ≥20 bpm	
	<50 bpm and decrease from baseline ≥10 bpm	
	<50 bpm and decrease from baseline ≥20 bpm	
	Tachycardia	Per HV grade 1, 2, 3, plus shift change
	>100 bpm	
	>115 bpm	
	>130 bpm	
	Increase from baseline ≥10 bpm	
	Increase from baseline ≥20 bpm	
	>100 bpm and increase from baseline ≥10 bpm	
	>100 bpm and increase from baseline ≥20 bpm	
PR	≥240 ms	
	≥300 ms	
	≥200 ms and increase from baseline ≥40 ms	
	≥200 ms and increase from baseline ≥100 ms	
QRS	>110 ms	
	>160 ms	
	Increase from baseline ≥20 ms	
	Increase from baseline ≥40 ms	
QTc		To be applied to any kind of QT correction formula.
Borderline	>450 ms (Male) and <500ms; >470 ms and <500ms (Female)	
Prolonged*	≥500 ms	
Additional		
	Increase from baseline	
	Increase from baseline >10 ms	
	Increase from baseline >20 ms	
	Increase from baseline >40 ms	
	Increase from baseline >60 ms	

Note: Based on CPMP 1997 guideline.

Table 11-12 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
HR	Same as above in ECG category	
SBP increased		809/770 analyses
	>140 mmHg	
	>160 mmHg	
	>10 mmHg increase from baseline	
	>20 mmHg increase from baseline	
	>140 mmHg & >10 mmHg increase from baseline	
	>140 mmHg & >20 mmHg increase from baseline	
	>160 mmHg & >10 mmHg increase from baseline	
	>160 mmHg & >20 mmHg increase from baseline	
SBP decrease		Per HV grade 1, 3, plus shift change
	<90 mmHg	
	<80 mmHg	
	>10 mmHg decrease from baseline	
	>20 mmHg decrease from baseline	
	<90 mmHg and >10 mmHg decrease from baseline	
	<90 mmHg and >20 mmHg decrease from baseline	
	<80 mmHg and >10 mmHg decrease from baseline	
	<80 mmHg and >20 mmHg decrease from baseline	

Table 11-12 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