VERTEX

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Final Analysis)

Methods

Protocol Number VX14-661-111, Version 4.0

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Exploratory Study to Evaluate Effects of VX-661 in Combination With Ivacaftor on Lung and Extrapulmonary Systems in Subjects Aged 18 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

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[redacted]

3 INTRODUCTION

This statistical analysis plan (SAP) Methods for the final analysis is based on the approved clinical study protocol (CSP), dated 4 November 2015, version 3.0, final electronic case report form (eCRF) completion guidelines, version 1.0, dated 30 September 2015, and approved eCRF, version 3.0, dated 8 December 2015.

Study VX14-661-111 is a Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Exploratory Study to Evaluate Effects of VX-661 in Combination with Ivacaftor on Lung and Extrapulmonary Systems in Subjects Aged 18 years and Older with Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation.

This SAP (Methods) documents the planned final statistical analysis of efficacy and safety endpoints defined in the study protocol of VX14-661-111. [redacted]

The Vertex Biometrics Department will perform the final statistical analysis of the efficacy and safety data; SAS® Version 9.2 Software [redacted] or higher will be used to generate all statistical outputs (tables, listings, figures and datasets).

The SAP (Methods) for the final analysis will be finalized and approved prior to the 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 OBJECTIVE

The study objective is to evaluate the clinical mechanisms of action in lung function and extrapulmonary systems of VX-661 in combination with IVA (VX-661/ivacaftor) in subjects with CF who are homozygous for the *F508del-CFTR* mutation.

As all endpoints in this study are considered exploratory, statistical significance on every endpoint is not required for study success.

5 STUDY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Key Efficacy Endpoints

- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline at Day 28
- Absolute change in mucociliary clearance (MCC) from baseline at Day 28
- Absolute change in gastrointestinal pH from baseline at Day 29
- Absolute change in sweat chloride from baseline at Day 29

[redacted]

5.2 Safety Endpoint

Safety and tolerability will be evaluated via the following assessments:

- Adverse events (AEs)
- Clinical laboratory values (hematology, serum chemistry, coagulation studies, vitamin levels, lipid panel, and urinalysis)
- Standard digital electrocardiograms (ECGs)
- Vital signs
- Pulse oximetry

6 STUDY DESIGN

6.1 Overview of Study Design

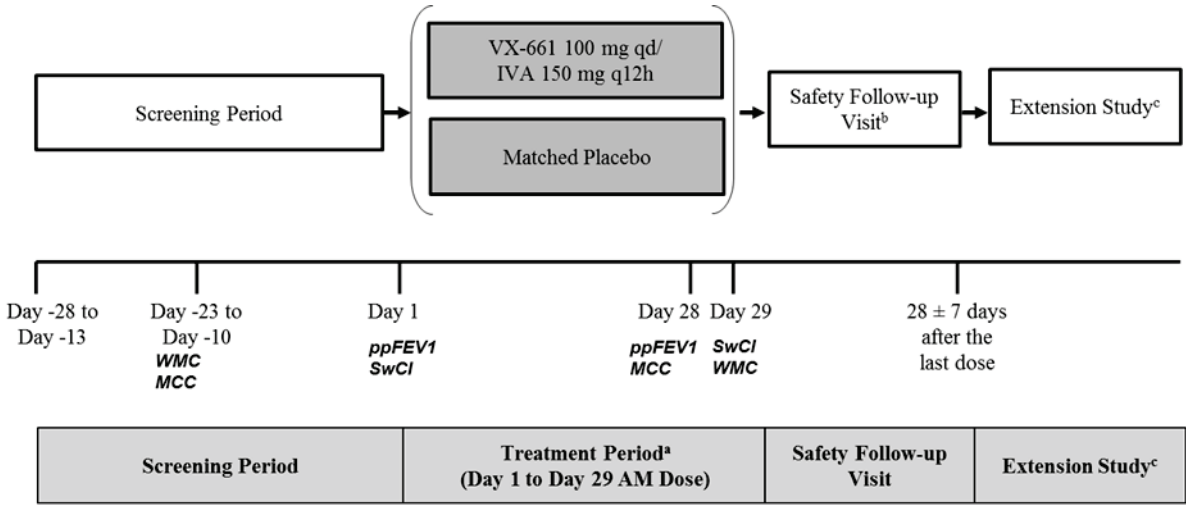
This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter, exploratory study in subjects with CF who are homozygous for the *F508del-CFTR* mutation. This study is designed to evaluate the lung function and extrapulmonary responses of subjects receiving VX-661/ivacaftor combination therapy.

This study includes a Screening Period, Treatment Period, and a Safety Follow-up Visit. The study plans to randomize a target of 35 subjects and up to approximately 45 subjects. Subjects will be randomized (4:1) to VX-661/ivacaftor or placebo, respectively, as shown in Figure 7-1.

Subjects who prematurely discontinue study drug treatment will be asked to complete assessments as described in the CSP.

Subjects who complete the Treatment Period and are eligible and elect to roll into an extension study will be required to have a Safety Follow-up visit 28 ± 7 days after the last dose of study drug.

Figure 6-1: Schematic of the Study Design



MCC: mucociliary clearance; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; WMC: wireless motility capsule.
Note: Only key assessments are included in the figure.
[a] Study drug will be administered for 29 day (± 3 days) and the last dose of study drug will be administered at the Day 29 Visit.
[b] The Safety Follow-up Visit is scheduled to occur 28 (± 7) days after the last dose of study drug for all subjects.
[c] Subjects who complete the Day 29 Visit and subsequently the Safety Follow-up Visit will be offered the opportunity to enroll in an extension study of VX-661/ivacaftor combination therapy if they meet eligibility requirements for the extension study.

6.2 Sample Size and Power

A target of at least 35 subjects, with up to approximately 45, who meet the eligibility criteria will be randomized in a ratio of 4:1 to active study drug or placebo to maximize power across the endpoints.

The objective of the study is to evaluate the clinical mechanisms of VX-661/ivacaftor combination therapy in both lung function and extrapulmonary systems in subjects with CF who are homozygous for the *F508del* mutation on the *CFTR* gene. For a subset of the key endpoints (specifically, MCC, and gastrointestinal pH, as captured in Table 7-2 and Table 7-3), no data are available for the *F508del* homozygous population. Therefore, data for both gastrointestinal pH and MCC were compiled from the G551D Observational (GOAL) Study[2] evaluating IVA monotherapy in patients with the *G551D-CFTR* mutation for the purpose of sample size calculation. Mean changes from baseline for gastrointestinal pH and MCC endpoints in the VX-661/ivacaftor combination therapy group were derived assuming approximately 50% of those observed for the active group in the observational

study. Standard deviations were assumed to be similar to those observed in the reference studies. For $ppFEV_1$ and sweat chloride endpoints, sample size assumptions were based on observed data from the Vertex VX11-661-101 study.

Based on these assumptions, a sample size of 36 subjects in the VX-661/ivacaftor combination therapy group (based on 45 subjects randomized 4:1) will provide adequate power to detect a statistically significant difference from baseline at Day 28 or 29 for the key endpoints, even after assuming that 10 % to 30% subjects may not have complete data through Day 29 (depending on the endpoint, based on estimates obtained from the GOAL study).

Table 6-1 through Table 6-4 display power estimates to detect an expected mean change from baseline (Δ) for key endpoint measures in the VX-661/ivacaftor combination therapy group based on a sample size of 36 subjects in the VX-661/ivacaftor group using a 2-sided paired *t*-test at a significance level of $\alpha = 0.05$. More specifically, the endpoint measures include $ppFEV_1$ at Day 28 (Table 6-1), percent whole lung mucus clearance through 60 minutes at Day 28 (Table 6-2), small bowel area under the curve (AUC) over 1-minute mean pH increments through 30 minutes after gastric emptying at Day 29 (Table 6-3), and sweat chloride at Day 29 (Table 6-4). Further, a sample size of 28 subjects in the VX661/ivacaftor combination therapy group (resulting in a total of 35 subjects including 7 subjects in the placebo group to achieve a 4:1 randomization ratio) will provide at least 80% power for each of the endpoints to detect the expected mean change from baseline with the expected standard deviation. Thus 35 to 45 subjects will be required to obtain a minimum of 80% to a maximum of >99% power across endpoints. Sample size calculations were performed using PASS 11 software, Version 11.0.2. Given the exploratory nature of this study, no multiplicity adjustment of type I error will be conducted for the analysis of key endpoints.

Table 6-1 Power for Within-Group Comparison (VX-661/ivacaftor combination therapy) for $ppFEV_1$ With N (VX-661/ivacaftor combination therapy) = 36 and $\Delta = 4.5\%$

Standard deviation	$\sigma = 7\%$ (expected)	$\sigma = 8\%$	$\sigma = 9\%$	$\sigma = 10\%$
Power	96%	91%	83%	75%
Power (10% missing data)	95%	88%	80%	71%
N (VX-661/ivacaftor combination therapy) for 80% power	21	27	34	41

Table 6-2 Power for Within-Group Comparison (VX-661/ivacaftor combination therapy) for Average % Whole Lung Clearance Through 60 Minutes With N (VX-661/ivacaftor combination therapy) = 36 and Δ = 6%

Standard deviation	σ = 6%	σ = 8% (expected)	σ = 10%	σ = 12%
Power	>99%	99%	94%	83%
Power (20% missing data)	>99%	97%	88%	74%
N (VX-661/ivacaftor combination therapy) for 80% power	10	16	24	34

Table 6-3 Power for Within-Group Comparison (VX-661/ivacaftor combination therapy) for Small Bowel AUC Over 1-minute Mean pH Increments Through 30 Minutes After Gastric Emptying With N (VX-661/ivacaftor combination therapy) = 36 and Δ = 22 pH Minutes (or Equivalently, 0.73 pH)

Standard deviation (pH mins)	σ = 20	σ = 24 (expected)	σ = 28	σ = 32
Power	>99%	>99%	>99%	98%
Power (30% missing data)	>99%	>99%	97%	92%
N (VX-661/ivacaftor combination therapy) for 80% power	9	12	15	19

Table 6-4 Power for Within-Group Comparison (VX-661/ivacaftor combination therapy) for Sweat Chloride With N (VX-661/ivacaftor combination therapy) = 36 and Δ = -5 mmol/L

Standard deviation (mmol/L)	σ = 5	σ = 6	σ = 7 (expected)	σ = 8
Power	>99%	>99%	99%	95%
Power (10% missing data)	>99%	>99%	98%	94%
N (VX-661/ivacaftor combination therapy) for 80% power	10	14	18	23

6.3 Randomization

A target of at least 35 subjects, with up to approximately 45, who meet the eligibility criteria will be randomized in a ratio of 4:1 (active study drug:placebo). An interactive web response system (IWRS) will be used to assign subjects to treatment using a list of randomization codes generated by a designated vendor [redacted]. The only Vertex personnel involved in developing the randomization

specifications and reviewing the dummy randomization code list was the Study Biostatistician (SB). The SB was blinded to the final randomization code list and the actual treatment assignments.

6.4 Blinding and Unblinding

This is a double-blind study.

6.4.1 Blinding

Blinding of treatment codes and applicable study data will be maintained until the database is locked for the final analysis.

The subjects and all site personnel, including the investigator, the site monitor, and the study team, will be blinded 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 SAE processing and reporting regulations
- Unblinded statistician preparing the final (production) randomization list, who is not part of the study team
- Vertex Clinical Operations IWRS management
- Vertex Clinical Supply Chain
- Vendor analyzing PK samples
- Vertex medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time

Vertex Drug Metabolism and Pharmacokinetics laboratory personnel will not be involved in the conduct of the study and will be unblinded to the bioanalysis results but will remain blinded to subject number and treatment assignment.

Spirometry Data Blinding

Despite treatment blinding, knowledge of the spirometry results has the potential to suggest whether a subject has been administered active study drug or placebo. Therefore, during the conduct of the study, the Vertex study team will have no access to the postdose spirometry results data. The vendor for central reading of the spirometry data will only send the blinded spirometry files (blinded treatment group, with real values for screening and baseline, but with dummy values for all the spirometry results data after baseline) to Vertex to be used for developing the statistical programs. Furthermore, subjects and their caregiver should not be informed of their study-related spirometry results during the Treatment Period regardless of whether the subject has prematurely discontinued treatment.

Sweat Chloride Data Blinding

Despite treatment blinding, knowledge of the sweat chloride data has the potential to suggest whether a subject has been administered active study drug or placebo. Therefore, during the conduct of the study, the Vertex study team will not have access to the sweat chloride data; dummy data will be used to develop statistical programs. During the process of locking the clinical database, after all study visits have been completed, access to treatment-blinded sweat chloride data will be provided to a small group of individuals who are not part of the Vertex study team. This group, which will consist of a biostatistician, a statistical programmer, a validation statistical programmer, and a clinical reviewer, will review the sweat chloride data to ensure there are no significant data issues and will use the blinded data set to refine the statistical programs.

MCC Blinding

Despite treatment blinding, knowledge of the MCC data has the potential to suggest whether a subject has been administered active study drug or placebo. Therefore, during the conduct of the study, the Vertex study team will have no access to the MCC data. Results data will be submitted to a central reader. These individuals, including site staff performing the MCC assessment, will otherwise not be involved in any other aspects of study conduct or subject interaction.

WMC Blinding

Despite treatment blinding, knowledge of the WMC data has the potential to suggest whether a subject has been administered active study drug or placebo. Therefore, during the conduct of the study, the Vertex study team will have no access to the WMC data, except confirmation that the WMC has passed. Results data will be submitted to the central reader, who will otherwise not be involved in any other aspects of study conduct or subject interaction.

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.

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 (FAS), and Safety Set.

The **All Subjects Set** will include all subjects who were randomized or dosed. This analysis set will be used for all individual subject data listings and the disposition summary table, unless specified otherwise.

The **Full Analysis Set (FAS)** will include all randomized subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug. The FAS will be used to summarize subject demographics and baseline characteristics, and for all efficacy analyses, unless specified otherwise.

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, with subjects analyzed according to the treatment they received, unless specified otherwise. If a subject received at least 1 dose of VX-661/IVA, the subject will be analyzed in the VX-661/IVA treatment group.

8 STATISTICAL ANALYSIS

8.1 General Considerations

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 subjects who were randomized or received at least 1 dose of study drug will be presented in individual subject data listings.

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

Categorical variables will be summarized using counts and percentages.

Baseline Value, unless specified otherwise, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug. For ECGs, the baseline value will be defined as the average of the non-missing pretreatment measurements (triplicate) on Day 1. For sweat chloride, the baseline value will be the mean of non-missing assessment values on the left and the right arms at the same time point that is the most recent time prior to the first dose of the study drug.

Change (Absolute Change) from baseline will be calculated as Postbaseline value - Baseline value.

Relative change from baseline will be calculated and expressed in percentage as 100%×(Postbaseline value - Baseline value)/Baseline value.

Treatment Emergent (TE) Period will include the time period starting from the first dose date of the study drug to the Safety Follow-up Visit. For subjects who do not have a Safety Follow-up Visit, the TE period will start from the first dose date of the study drug to 28 days after the last dose date of the study drug. The TE period will be used for safety analyses unless specified otherwise.

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.

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: No multiplicity adjustment will be performed for hypothesis testing.

8.2 Background Characteristics

8.2.1 Subject Disposition

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

- All Subjects
- Randomized
- Full Analysis Set (FAS)
- Safety Set

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

- Completed treatment period
- Prematurely discontinued the treatment and the reason for discontinuation
- Completed study (i.e., completed Safety Follow-up Visit)
- Prematurely discontinued the study and the reason for discontinuation
- Enrolled in a rollover extension study

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

8.2.2 Demographics and Baseline Characteristics

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

Demographic data will include the following:

- Age (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, Not collected per local regulations, and Other)

Baseline characteristics will include the following:

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

Disease characteristics will include the following:

- Percent predicted FEV_1 at baseline
- Sweat chloride at baseline
- Whole lung mucus clearance through 60 minutes at baseline
- Small bowel AUC over one-minute mean pH increments through 30 minutes after gastric emptying at baseline
- Use of dornase alfa (Yes, No)
- Use of inhaled antibiotic (Yes, No)
- Use of any bronchodilator (Yes, No)
- Use of any inhaled bronchodilator (Yes, No)
- Use of any inhaled hypertonic saline (Yes, No)
- Use of any inhaled corticosteroids (Yes, No)

[redacted]

A summary of medical history will be provided. In addition, the number of subjects reported to have had positive cultures for respiratory pathogens in 2 years prior to screening will be summarized by test and categories.

8.2.3 Prior and Concomitant Medications

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

- Prior medication: any medication that started before the first dose 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 TE 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.

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, 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.

Post-treatment medications will be listed by subject.

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

8.2.4 Study Drug Exposure

Duration of study drug exposure (in days) will be calculated as follows: last dose date – first dose date + 1 day, regardless of any study drug interruption

Exposure summaries will be based on the FAS.

8.2.5 Study Drug Compliance

Study drug compliance based on number 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 based on study drug exposure 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 both VX-661/ivacaftor and Ivacaftor doses on that day.

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

Study drug compliance summaries will be based on the FAS.

8.2.6 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that has the potential to affect the interpretation of study results. All IPDs will be derived from a subset of major and minor deviations and will be identified from the clinical database and/or site deviation log. The rules for identifying IPDs will be included in an internal Biometrics document.

All IPDs will be presented in an individual subject data listing.

8.3 Efficacy Analysis

As all endpoints in this study are considered exploratory, statistical significance on every endpoint is not required for study success.

Unless otherwise defined, all efficacy analyses described in this section will be based on the FAS. The analysis will include all available measurements up to Day 29 [inclusive], including measurements after treatment discontinuation, per the visit windowing rules described in Appendix B.

[redacted]

8.3.1 Analysis of Key Efficacy Variables

The key efficacy variables are:

- Absolute change in ppFEV$_1$ from baseline at Day 28
- Absolute change in average percent whole lung clearance through 60 minutes from baseline at Day 28
- Absolute change in small bowel AUC over 1-minute mean pH increments through 30 minutes after gastric emptying from baseline at Day 29
- Absolute change in sweat chloride from baseline at Day 29

For each variable, a paired t-test will be performed to test the null hypothesis of a zero mean change from baseline within the VX-661/ivacaftor combination therapy group.

a) The paired t-test analysis will be performed assuming a normal distribution for the paired differences within the VX-661/ivacaftor combination therapy group. Further, any missing data will be assumed to be missing completely at random, independently of the observed data. The within-group test will be based on a 2-sided paired t-test performed at $\alpha = 0.05$.

b) The results from this analysis will include the observed mean change from baseline, a 95% CI, and a 2-sided p-value for a test of the null hypothesis of a zero mean change from baseline.

A descriptive analysis that includes the observed mean change from baseline at Day 28 or Day 29 and 95% CI will also be presented for the placebo group. A paired t-test may be performed for supportive analysis.

Further, a descriptive analysis of observed values and change from baseline values at each scheduled time point will be presented by treatment group.

[redacted]

[redacted]

No missing data sensitivity analyses will be performed for this 29-day treatment duration study.

8.3.1.1 Absolute change in ppFEV1 from baseline at Day 28

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 Hankinson[1] standard for subjects aged 18 years and older with details provided in Appendix E.

The paired t-test analysis will be performed to test the null hypothesis of a zero mean change from baseline within the VX-661/ivacaftor combination therapy group.

A descriptive analysis that includes the observed mean change from baseline at Day 28 and 95% CI will also be presented for the placebo group. A paired t-test may be performed for supportive analysis.

[redacted]

Descriptive statistics of observed values and change from baseline values at each scheduled visit will be presented by treatment group.

8.3.1.2 Absolute Change in average percent whole lung clearance through 60 minutes from baseline at Day 28

Average percent whole lung clearance through 60 minutes will be calculated as the average of non-missing percent lung clearance values from the whole lung (decay and background corrected) reported at 10 minutes through 60 minutes by 10 minute increments. [redacted]

The paired t-test analysis will be performed to test the null hypothesis of a zero mean change from baseline within the VX-661/ivacaftor combination therapy group.

A descriptive analysis that includes the observed mean change from baseline at Day 28 and 95% CI will also be presented for the placebo group. A paired t-test may be performed for supportive analysis.

[redacted]

Descriptive statistics of observed values and change from baseline values of percent whole lung clearance at each scheduled visit will be presented by treatment group.

8.3.1.3 Absolute Change in small bowel AUC over 1-minute mean pH increments through 30 minutes after gastric emptying from baseline at Day 29

Small bowel AUC over 1-minute mean pH increments through 30 minutes after gastric emptying will be calculated as the area under the 1-minute interval small bowel pH profile through 30 minutes after gastric emptying based on the trapezoidal rule. The 1–minute mean pH values will be calculated as the average of the 5-second pH measurements obtained within each minute through 120 minutes after gastric emptying. [redacted]

The paired t-test analysis will be performed to test the null hypothesis of a zero mean change from baseline within the VX-661/ivacaftor combination therapy group.

A descriptive analysis that includes the observed mean change from baseline at Day 29 and 95% CI will also be presented for the placebo group. A paired t-test may be performed for supportive analysis.

[redacted]

8.3.1.4 Absolute Change in sweat chloride from baseline at Day 29

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. A volume ≥15 µL is required for an accurate determination of sweat chloride. Any results reported 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 paired t-test analysis will be performed to test the null hypothesis of a zero mean change from baseline within the VX-661/ivacaftor combination therapy group.

A descriptive analysis that includes the observed mean change from baseline at Day 29 and 95% CI will also be presented for the placebo group. A paired t-test may be performed for supportive analysis.

[redacted]

Descriptive statistics of observed values and change from baseline values at each scheduled visit will be presented by treatment group.

[redacted]

[redacted]

8.4 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, serum chemistry, coagulation studies, vitamin levels, lipid panel, 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.

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

8.4.1 Adverse Events

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

- Pretreatment AE: any AE that started before the first dose date of study drug
- TEAE: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug through the end of the TE period
- 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 H.

AE summary tables will be presented for TEAEs only, overall and by treatment group, and will include the following:

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- TEAEs leading to death

Summaries will be presented by MedDRA system organ class and preferred term using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries.

In addition, a listing containing individual subject adverse event data for TEAEs leading to treatment discontinuation, SAEs and deaths will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in an individual subject data listing.

8.4.2 Clinical Laboratory

For treatment emergent laboratory measurements, the raw values and change from baseline values of the continuous hematology, chemistry, and coagulation studies will be summarized in SI units by treatment group at each scheduled visit.

The number and percentage of subjects with at least one threshold analysis laboratory event during the TE period will be summarized overall and by treatment group, including the shift of the threshold analysis event from baseline to post baseline. The threshold analysis criteria are provided in Appendix H.

For each 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.

A listing of subjects with elevated LFT results during the TE period will be presented based on any of the following: AST>3 × ULN, ALT>3 × ULN, ALP >1.5 × ULN, or total bilirubin >2 × ULN. For each subject in the listing, LFT assessments at all time points will be included (scheduled and unscheduled).

Results of vitamin levels and lipid panel will be summarized by treatment group and visit.

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

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

8.4.3 Standard 12-Lead Electrocardiogram

For treatment-emergent ECG measurements, a summary of raw values and change from baseline values will be provided by treatment group and visit for the following standard 12-lead ECG measurements: RR (ms), HR (beats per minute), PR (ms), QRS duration (ms), QRX axis (degrees), QT (ms), and QT corrected for HR [QTcF (ms)].

The number and percentage of subjects with at least one threshold analysis ECG event during the TE period will be summarized overall and by treatment group. The threshold analysis criteria are provided in Appendix H.

8.4.4 Vital Signs

For treatment-emergent vital signs measurements, the raw values and change from baseline values will be summarized by treatment group and visit: systolic and diastolic blood pressure (mm Hg), body temperature (^{o}C), HR (beats per minute), and respiratory rate (breaths per minute).

The number and percentage of subjects with at least one threshold analysis vital signs event during the TE period will be summarized overall and by treatment group. The threshold analysis criteria are provided in Appendix H.

8.4.5 Pulse Oximetry

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

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 will be summarized overall and by treatment group.

8.4.6 Physical Examination

PE findings will be presented as a data listing only.

9 INTERIM AND DMC ANALYSES

9.1 Interim Analysis

Not applicable.

9.2 DMC Analysis

Not applicable.

10 REFERENCES

[1] Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999; 159:179-87.

[2] Rowe SM, Heltshe SL, Gonska T, Donaldson SH, Borowitz D, Gelfond D, et al. Clinical mechanism of the cystic fibrosis transmembrane conductance regulator potentiator ivacaftor in G551D-mediated cystic fibrosis. Am J Respir Crit Care Med. 2014;190(2):175–184.

11 APPENDICES

Appendix A Schedule of Assessments

Schedules of Assessments are shown in Table 12-1 (Screening Period) and Table 12-2 (Treatment Period through the Safety Follow-up Visit).

All visits are to be scheduled relative to the Day 1 Visit (first dose of study drug).

Table 11-1 Study VX14-661-111: Screening Period

Assessment	Screening Period Day -28 through Day -1			
	Screening Visit Day -28 to Day -13	**Telephone Contact 2 Days After Patency Capsule Administration**	**Clinic Visit Day -23 to -10[a]**	**Telephone Contact 5 Days After WMC Administration**
Clinic visit	X		X[b]	
Informed consent	X			
Inclusion/exclusion criteria review	Continuous from signing of informed consent form (ICF) before randomization[a]			
Demographics	X			
Medical history	X			
Ophthalmologic history	X			
CF genotype[c]	X			
Weight, height[d]	X			

[a] Clinic Visit Day -23 through Day -10 will take place only if a subject passes the patency capsule test. Select baseline assessments are performed on Day -23 through Day -10, and the remaining are performed on Day 1. Before any baseline assessments are performed, eligibility for enrollment based on all available screening assessment results must be verified by the investigator.

[b] This visit may occur on 1 day or on 2 separate days.

[c] All subjects will be tested for CF genotype. The CF genotype sample will be taken during the Day -28 to Day -13 Visit. Confirmation of the genotype will be required before randomization.

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

Table 11-1 Study VX14-661-111: Screening Period

Assessment	Screening Period Day -28 through Day -1			
	Screening Visit Day -28 to Day -13	**Telephone Contact 2 Days After Patency Capsule Administration**	**Clinic Visit Day -23 to -10[a]**	**Telephone Contact 5 Days After WMC Administration**
Complete physical examination	X			
Ophthalmologic examination[e]	Between signing of ICF and randomization			
Standard 12-lead ECG[f]	X			
Vital signs[g]	X			
Pulse oximetry[g]	X			
Spirometry	X[h]		X[i]	
Urinalysis	X			
Serum FSH[j] (postmenopausal female subjects only)	X			
Pregnancy test[k]	Serum		Urine[l]	

[e] One ophthalmologic examination will be conducted by a licensed ophthalmologist during the Screening Period. The ophthalmologic examination does not need to be repeated if there is documentation of an examination that met the protocol criteria and that was conducted within 3 months before the Screening Period. Subjects with clinically significant cataracts, lens opacity, Y-suture, or lamellar rings will be excluded.

[f] A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes. ECGs will be performed before vital signs, pulse oximetry, and any other procedures that may affect heart rate (e.g., blood sampling).

[g] Vital signs and pulse oximetry will be collected after the subject has been at rest (seated or supine) for 5 minutes. Vital signs will be performed after ECGs and before blood sampling.

[h] Spirometry may be performed pre- or postbronchodilator.

[i] Spirometry should be performed prebronchodilator, on the same day as the MCC assessment, and prior to both WMC and MCC if both are done on the same day.. Spirometry values must be ≥30 percent predicted FEV1 before MCC.

[j] FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be ≥40 mIU/mL to be considered postmenopausal.

[k] Pregnancy tests will be performed for all female subjects of childbearing potential.

Table 11-1 Study VX14-661-111: Screening Period

Assessment	Screening Period Day -28 through Day -1			
	Screening Visit Day -28 to Day -13	**Telephone Contact 2 Days After Patency Capsule Administration**	**Clinic Visit Day -23 to -10[a]**	**Telephone Contact 5 Days After WMC Administration**
Sweat chloride[m]	X			
Hematology	X			
Coagulation	X			
Serum chemistry	X			
Patency capsule	X[n]	Confirm passage[o]		
Meal or snack at site			X[p]	
WMC[q]			X[r]	confirm passage[s]

[l] Pregnancy test results will be obtained before administration of WMC and the MCC assessment. If the Clinic Visit Day -23 to -10 occurs on 2 separate days, pregnancy testing will occur before the procedures on each day.

[m] Sweat chloride test is not required if the subject has a documented sweat chloride test result in the medical records.

[n] All subjects will be administered a patency capsule test at the Day -28 to Day -13 Screening Visit after all other assessments have been completed. Subjects will stay under observation in the clinic for 2 hours after administration of the patency capsule.

[o] Telephone contact will occur 2 days after administration of the patency capsule to confirm passage of the patency capsule in the stool (unless the subject confirms passage of the capsule prior to the scheduled telephone contact). A subject must pass the patency capsule test to continue the Screening Period assessments. If passage of the patency capsule is not confirmed during the telephone contact, the subjects must return to the clinic and the medical monitor must be contacted immediately (see the Study Reference Manual for additional information).

[p] Subjects must adhere to study restrictions in the CSP regarding meals. During the Clinic Visit on Day -23 to Day -10, subjects will fast for 8 hours (water is permitted) before administration of a snack bar (in place of the morning meal), and for an additional 4 hours immediately following administration of the WMC. If the Day -23 to – 10 Visit occurs on 2 separate days, a meal or snack bar will be provided at the clinic on both days.

[q] If MCC and WMC administration occur on a single day, WMC administration should be completed before the MCC assessment.

[r] Subjects must pass the patency capsule test and adhere to WMC restrictions in the CSP before administration of the WMC. Subjects will fast for 8 hours (water is permitted) before administration of a snack bar (in place of the morning meal) with the WMC, and will fast for an additional 4 hours immediately following administration of the WMC. All screening assessments, except for the ophthalmologic examination [redacted], must be completed before the WMC.

Table 11-1 Study VX14-661-111: Screening Period

Assessment	Screening Period Day -28 through Day -1			
	Screening Visit Day -28 to Day -13	**Telephone Contact 2 Days After Patency Capsule Administration**	**Clinic Visit Day -23 to -10[a]**	**Telephone Contact 5 Days After WMC Administration**
MCC[t]			X	
[redacted]	[redacted]			
Prior and concomitant medications	Continuous from signing of ICF through Safety Follow-up Visit			
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit			

CF: cystic fibrosis; ECG: electrocardiogram; FSH: follicle-stimulating hormone; MCC: mucociliary clearance; WMC: wireless motility capsule

[s] Telephone contact will occur 5 days after the administration of the WMC to evaluate passage of the capsule (unless the subject confirms the passage of the capsule prior to the scheduled contact). If passage of the WMC is not confirmed during the telephone contact, the medical monitor must be contacted immediately to confirm further course of action. Subjects will not be randomized in the study until passage of the WMC has been confirmed by the central reader or X-ray, regardless of confirmation of passage by subject at telephone contact.

[t] Bronchodilator usage is restricted for 12 hours before the MCC assessment. The first MCC scan will be immediately following radiolabeled aerosol inhalation, and the second scan 6 hours (± 30 minutes) after inhalation. Subjects will adhere to study restrictions in the CSP related to MCC (see the Study Reference Manual for additional information).

[redacted]

Table 11-2 Study VX14-661-111: Treatment Period and Safety Follow-Up Visit

Event/Assessment[a]	Treatment Period				Telephone Contact 5 Days After WMC Administration	Early Treatment Termination[b] Visit	Safety Follow-up Visit 28 (± 7) Days After Last Dose of Study Drug
	Day 1	Day 14 (± 3 days)	Day 28 (± 3 days)[c]	Day 29 (± 3 days)			
Clinic visit	X		X[d]	X		X	X
Telephone contact		X[e]			X		
Inclusion and exclusion criteria review[f]	X						
Weight and Height[g]	X		X			X (weight)	X
Complete physical examination[h]	X						X
Standard 12-lead ECG [i]	X[j]			X[j]		X[j]	X[j]
Vital signs[k]	X		X	X		X	X

[a] All assessments will be performed before administration of study drug unless noted otherwise.

[b] If the subject prematurely discontinues study treatment, an Early Treatment Termination (ETT) Visit should be scheduled as soon as possible after the last dose of study drug. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (± 7) days after their last dose of study drug. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT will not be required.

[c] This visit may occur on 1 day or on 2 separate days. All assessments of the Day 28 Visit must be completed before the Day 29 Visit assessments.

[d] Subjects will be offered the option of an overnight stay in proximity to the clinic between Days 28 and 29.

[e] A telephone contact will occur on Day 14 to review adverse events (AEs) and concomitant medications.

[f] Confirmation of subject eligibility will occur before randomization.

[g] Weight and height will be measured before dosing with shoes off. Height will be collected only for subjects 21 years of age or younger at the Day 1, Day 28, and Safety Follow-up Visits.

[h] A complete physical examination will occur on Day 1 and at the Safety Follow-up Visit. Symptom-targeted physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

[i] All ECGs will be performed before vital signs, pulse oximetry, and any other procedures that may affect heart rate (e.g., blood sampling). Subjects must be supine for at least 5 minutes before the start of the ECG.

[j] At the Day 1 and Day 29 Visits, ECGs will be collected before dosing and at 1.5 and 3 hours after the morning dose of study drug. ECGs collected on Day 1 before dosing will be performed in triplicate. If study drug is not administered on the Day of the visit (i.e., because of study drug interruption or permanent discontinuation of study drug), only 1 ECG will be collected.

Event/Assessment[a]	Treatment Period				Telephone Contact 5 Days After WMC Administration	Early Treatment Termination[b] Visit	Safety Follow-up Visit 28 (± 7) Days After Last Dose of Study Drug
	Day 1	Day 14 (± 3 days)	Day 28 (± 3 days)[c]	Day 29 (± 3 days)			
Pulse oximetry[k]	X		X	X		X	X
Spirometry[l]	X		X			X	X
[redacted]	[redacted]		[redacted]				
Urinalysis	X			X		X	X
Sweat chloride[n]	X			X			
Pregnancy test[o]	Urine		Urine	Serum		Serum	X[p]
VX-661 and M1-661 PK[q]			X	X		X	X
IVA and M1-IVA PK[q]			X	X		X	X
Hematology	X			X		X	X
Coagulation	X			X		X	X

k Vital signs and pulse oximetry will be collected before dosing and after the subject has been at rest (seated or supine) for at least 5 minutes. Vital signs will be performed after ECGs and before blood sampling.

l Spirometry will be performed before the MCC assessment and study drug dosing, and must be prebronchodilator. At the Day 28 Visit, bronchodilator usage is restricted for 12 hours before the MCC assessment. If the Day 28 Visit assessments occur on 2 separate days, spirometry should be performed on the same day as and preceding the MCC assessment.

[redacted]

n Sweat collection will occur before the morning dose and no more than 1 hour before the predose PK sample collection. Sweat chloride assessments will not overlap with the collection of other assessments (see the Laboratory Manual for additional information).

o Pregnancy tests will be performed for all female subjects of childbearing potential. Pregnancy test results must be obtained before randomization at Day 1 and before the MCC assessment at Day 28.

p Serum pregnancy test must be performed at the Safety Follow-up Visit for subjects who discontinue the study and the Safety Follow-up Visit replaces the ETT Visit for subjects who complete the study and chose not to enroll in the extension study. Urine pregnancy test must be performed for subjects who complete Day 29 and chose to enroll in the extension study or for subjects who discontinue the study and complete both ETT and Safety Follow-up Visits.

q Single PK blood samples will be collected within 60 minutes before the morning dose of study drug at Day 28 and Day 29. If study drug is not administered at the visit (i.e., study drug interruption or permanent discontinuation of study drug), a PK blood sample will still be collected. At the ETT (as applicable) and the Safety Follow-up Visit, a single PK blood sample will also be collected.

Event/Assessment[a]	Treatment Period				Telephone Contact 5 Days After WMC Administration	Early Treatment Termination[b] Visit	Safety Follow-up Visit 28 (± 7) Days After Last Dose of Study Drug
	Day 1	Day 14 (± 3 days)	Day 28 (± 3 days)[c]	Day 29 (± 3 days)			
Serum chemistry	X			X		X	X
Lipid panel[r]	X			X		X	X
Vitamin levels	X			X		X	X
[redacted]	[redacted]						
[redacted]	[redacted]						
[redacted]	[redacted]		[redacted]			[redacted]	[redacted]
[redacted]	[redacted]		[redacted]				
Wireless motility capsule (WMC)				X[s]	Confirm passage[t]		
Mucociliary clearance assessment (MCC)[u]			X				
Adverse events and concomitant medications	Continuous from signing of ICF through Safety Follow-up Visit						

[r] Blood samples for lipid panel tests will be collected after fasting for a minimum of 4 hours.

[s] Subjects will adhere to study restrictions in the CSP related to WMC. During the Day 29 Visit, subjects will fast for 8 hours (water is permitted) before administration of a snack bar (in place of the morning meal) with the WMC and the morning dose of study drug , and will fast for an additional 4 hours immediately following administration of the WMC.

[t] Telephone contact will occur 5 days after the administration of the WMC to confirm passage of the capsule. If passage of the WMC is not confirmed by the telephone contact, the medical monitor must be contacted immediately to confirm further course of action. Passage of the WMC must be confirmed by the central reader or X-ray, regardless of confirmation of passage by subject at telephone contact.

[u] On Day 28, radiolabeled aerosol inhalation will occur after the dose of study drug. One MCC scan will occur immediately following radiolabeled aerosol inhalation and a second scan approximately 6 hours (± 30 minutes) after inhalation. Subjects will adhere to study restrictions in the CSP related to MCC (see the Study Reference Manual for additional information).

Event/Assessment[a]	Treatment Period				Telephone Contact 5 Days After WMC Administration	Early Treatment Termination[b] Visit	Safety Follow-up Visit 28 (± 7) Days After Last Dose of Study Drug
	Day 1	Day 14 (± 3 days)	Day 28 (± 3 days)[c]	Day 29 (± 3 days)			
Randomization[v]	X						
Meal(s) or snack(s) at site[w]	X		X	X[x]			
Study drug dosing[y]	X						
Study drug count	X		X	X		X	X[z]

CF: cystic fibrosis; ECG: electrocardiogram; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; [redacted]; MCC: mucociliary clearance; PK: pharmacokinetics; WMC: wireless motility capsule

[v] Randomization must occur after all inclusion and exclusion criteria are met and before the first dose of study drug. Randomization may occur on Day -1.

[w] Fat-containing food such as a "standard CF" high-fat, high-calorie meal or snack will be provided at the site to subjects after all predose assessments have occurred (if the Day 28 assessments occur on 2 separate days, a meal or snack will be provided for each clinic visit.).

[x] Administration of a snack bar (in place of the morning meal).

[y] Study drug will be administered as described in the CSP. On Day 1 through the morning of the Day 29 Clinic Visit, study drug will be administered within 30 minutes of starting a meal with fat-containing food such as a "standard CF" high-fat, high-calorie meal or snack. At the Day 29 Visit, subjects will receive a snack bar in place of the morning meal. On days of scheduled visits, the morning dose of study drug will be administered at the site after the last predose assessment has been completed.

[z] Study drug count will occur at the Safety Follow-up Visit for all subjects who discontinue the study and for whom the Safety Follow-up Visit replaces the ETT.

Appendix B Analysis Visit Window Mapping Rules for Safety and Efficacy Assessments

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

Safety Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window[c] (in study days)
Hematology Serum Chemistry Coagulation Urinalysis Lipids Vitamin Levels	Baseline	1	≤ 1
	Day 29	29	[2, 43]
	Safety Follow-up	57	Use nominal visit
Standard 12-Lead ECG	Baseline	Day 1	1
	Day 1 (1.5 hours and 3 hours post morning dose)	Day 1 (1.5 hours and 3 hours post morning dose)	Use nominal visit
	Day 29 (before, 1.5 hours and 3 hours post morning dose)	Day 29 (before, 1.5 hours and 3 hours post morning dose)	Use nominal visit
	Safety Follow-up	57	Use nominal visit
Vital Signs Pulse Oximetry	Baseline	1	≤ 1
	Day 28	28	Use nominal visit
	Day 29	29	Use nominal visit
	Safety Follow-up	57	Use nominal visit
Weight and Height	Baseline	1	≤ 1
	Day 28	28	[2, 42]
	Safety Follow-up	57	Use nominal visit

When a subject is lost to follow up and last dose date is unknown, impute last dose date of all study drugs as last on-treatment visit date.

[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.
[c]For an early treatment discontinuation, Day 28 is last dose date -1, and Day 29 = last dose date of all study drugs.

Efficacy Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window[c] (in study days)
Spirometry	Day -23 to Day -10	Use nominal visit	Use nominal visit
	Baseline	1	≤1
	Day 28	28	[2, 42]
Sweat Chloride	Baseline	1	≤1
	Day 29	29	[2, 43]
Wireless Motility Capsule (WMC)	Baseline	Day -23 to Day -10	≤1
	Day 29	29	[2, 43]
Mucociliary Clearance (MCC)	Baseline	Day -23 to Day -10	< 1
	Day 28	28	[2, 42]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

When a subject is lost to follow up and last dose date is unknown, impute last dose date of all study drugs as last on-treatment visit date.

[a]Visit name is used to report data in tables, listings and figures.
[b]Target day time point is predose.
[c]For an early treatment discontinuation, Day 28 is last dose date - 1, and Day 29 = last dose date of all study drugs.

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

1) If no numerical measurement is available within a visit window, the measurement will be considered missing for the visit;
2) If there is more than one numerical measurement available within the same visit window, use the following rules:

a) For **efficacy** parameters: if there are multiple measurements within a visit window, the measurement at the scheduled visit will be used. Otherwise,

   i. If there are no measurements at the scheduled visit, then the measurement closest to the target day will be used; or

ii. If there are multiple measurements with the same distance to the target day, the latest measurement will be used.

b) For **safety** parameters: if there are multiple measurements within a visit window,

i. The measurement closest to the target day will be used; or

ii. If there are multiple measurements within the same distance from the target day, the latest measurement will be used.

iii. For tables of the extreme lab measurement based on ULN or LLN, convert the lab measurements into times of ULN or LLN first, and then select the extreme measurement.

Derived Variables

1. Age (in years) at first dose date

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

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

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

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

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

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 (Early Treatment Termination visit date, last study drug administration date from EX SDTM domain, excluding PK dosing dates).

Appendix C Imputation Rules for Missing or Partial Start/Stop Dates of Concomitant Medications

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 prior to the first dose date.
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 summary, the prior, concomitant or post categorization of a medication is described in Table 12-10 below.

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

	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

Appendix E Coefficients for Hankinson Method for Calculating Predicted Spirometry Parameters

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 (L) will be calculated using the Hankinson[1] standard.

The Hankinson standard is designed for application to male subjects 18 years and older and female subjects 16 years and older. In this study, the standard will be applied for males and females aged 18 years and older per the study eligibility criteria.

Hankinson Normal Values (HNVs) will be calculated for FEV_1, forced vital capacity (FVC), forced expiratory flow mid expiratory phase ($FEF_{25-75\%}$), and FEV_1/FVC% using the Hankinson equation:

$$\text{Predicted lung function parameter} = b0+b1 \times age+b2 \times age^2+ b3 \times height^2$$

In the equation, height is given in centimeters, age is given in years, and the coefficients b_0, b_1, b_2, and b_3 are determined based on subject's sex, race, and age group as shown in Table 12-5. The 'White' race is handled as 'Caucasian' and all non-White race categories including 'Asian', 'American Indian or Alaska Native', 'Native Hawaiian or Other Pacific Islander', 'Not collected per local regulations', and 'Other', are handled as 'African American'.

If either height or age is missing, and the spirometry measurement is non-missing, the last non-missing value of height and age will be used in the calculation of predicted values.

Table 11-5 HNVs Equation Coefficients by Sex, Race, and Age

Parameter	Sex	Race	Age (years)	b_0	b_1	b_2	b_3
HNV_{FEV1}	Male	Caucasian	<20	-0.7453	-0.04106	0.004477	0.00014098
			≥20	0.5536	-0.01303	-0.000172	0.00014098
		African American	<20	-0.7048	-0.05711	0.004316	0.00013194
			≥20	0.3411	-0.02309		0.00013194
		Mexican American	<20	-0.8218	-0.04248	0.004291	0.00015104
			≥20	0.6306	-0.02928		0.00015104
	Female	Caucasian	<18	-0.8710	0.06537		0.00011496
			≥18	0.4333	-0.00361	-0.000194	0.00011496
		African American	<18	-0.9630	0.05799		0.00010846
			≥18	0.3433	-0.01283	-0.000097	0.00010846
		Mexican American	<18	-0.9641	0.06490		0.00012154
			≥18	0.4529	-0.01178	-0.000113	0.00012154
HNV_{FVC}	Male	Caucasian	<20	-0.2584	-0.20415	0.010133	0.00018642
			≥20	-0.1933	0.00064	-0.000269	0.00018642
		African American	<20	-0.4971	-0.15497	0.007701	0.00016643
			≥20	-0.1517	-0.01821		0.00016643
		Mexican American	<20	-0.7571	-0.09520	0.006619	0.00017823
			≥20	0.2376	-0.00891	-0.000182	0.00017823
	Female	Caucasian	<18	-1.2082	0.05916		0.00014815
			≥18	-0.3560	0.01870	-0.000382	0.00014815
		African American	<18	-0.6166	-0.04687	0.003602	0.00013606
			≥18	-0.3039	0.00536	-0.000265	0.00013606
		Mexican American	<18	-1.2507	0.07501		0.00014246
			≥18	0.1210	0.00307	-0.000237	0.00014246
$HNV_{FEF25-75\%}$	Male	Caucasian	<20	-1.0863	0.13939		0.00010345
			≥20	2.7006	-0.04995		0.00010345
		African American	<20	-1.1627	0.12314		0.00010461
			≥20	2.1477	-0.04238		0.00010461
		Mexican American	<20	-1.3592	0.10529		0.00014473
			≥20	1.7503	-0.05018		0.00014473
	Female	Caucasian	<18	-2.5284	0.52490	-0.015309	0.00006982
			≥18	2.3670	-0.01904	-0.000200	0.00006982
		African American	<18	-2.5379	0.43755	-0.012154	0.00008572
			≥18	2.0828	-0.03793		0.00008572
		Mexican American	<18	-2.1825	0.42451	-0.012415	0.00009610
			≥18	1.7456	-0.01195	-0.000291	0.00009610
$HNV_{FEV1/FVC\%}$	Male	Caucasian		88.066	-0.2066		

	African American	89.239	-0.1828
	Mexican American	90.024	-0.2186
Female	Caucasian	90.809	-0.2125
	African American	91.655	-0.2039
	Mexican American	92.360	-0.2248

Source: Reference: Hankinson (Tables 4, 5 and 6).

Appendix H Imputation Rules for Missing or Partial AE Start Date

Imputation rules for missing or partial AE start date are defined below:

1) If only Day of AE start date is missing:

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

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

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

2) If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

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

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

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

Appendix I Criteria for Threshold Analysis Events

Table 11-6 Threshold Criteria for Laboratory Tests (as applicable)

Parameter	Criteria	Comments
Clinical Chemistry		
CPK	>ULN - ≤ 2.5 x ULN >2.5 - ≤ 5 x ULN >5 - ≤ 10x ULN >10 x ULN	CTCAE grades 1-4
Creatinine	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	CTCAE grades 1-4
Blood Urea Nitrogen	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	Same criteria as creatinine No CTCAE
Sodium	Hyponatremia <LLN - ≥130 mmol/L <130 – ≥120 mmol/L <120 mmol/L	CTCAE grade 1, 3, 4 (No CTCAE grade 2)
	Hypernatremia >ULN - ≤ 150 mmol/L >150 mmol/L- ≤155 mmol/L >155 mmol/L - ≤ 160 mmol/L >160 mmol/L	CTCAE grade 1-4
Potassium	Hypokalemia <LLN – ≥ 3.0 mmol/L <3.0 – ≥ 2.5 mmol/L <2.5 mmol/L	CTCAE grade 1&2, 3, 4 (Grade 1 and 2 are the same)
	Hyperkalemia >ULN – ≤ 5.5 mmol/L >5.5 – ≤ 6.0 mmol/L >6.0 – ≤ 7.0 mmol/L >7.0 mmol/L	CTCAE grade 1-4
Total Cholesterol	>ULN – ≤ 7.75 mmol/L >7.75 – ≤ 10.34 mmol/L >10.34 – ≤ 12.92 mmol/L >12.92 mmol/L	CTCAE grade 1-4
Triglycerides	>1.71 – ≤ 3.42 mmol/L >3.42 – ≤ 5.7 mmol/L >5.7 – ≤ 11.4 mmol/L >11.4 mmol/L	CTCAE grade 1-4
Glucose	Hypoglycemia <3.0 – ≥ 2.2 mmol/L <2.2 - ≥ 1.7 mmol/L <1.7 mmol/L	CTCAE grade 1-4
	Hyperglycemia >ULN - ≤ 8.9 mmol/L >8.9 – ≤ 13.9 mmol/L >13.9 – ≤ 27.8 mmol/L	CTCAE grade 1-4

	>27.8 mmol/L	
Albumin	<35 - ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4
Lipase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4
Direct bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	Same Criteria as Total Bilirubin No CTCAE Not in DILI Guidance
GGT	>ULN - ≤ 2.5 x ULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	CTCAE grade 1-4
Calcium	Hypercalcemia >ULN - ≤ 2.9 mmol/L >2.9 – ≤ 3.1 mmol/L >3.1 – ≤ 3.4 mmol/L >3.4 mmol/L	CTCAE grade 1-4
	Hypocalcemia <LLN - ≥ 2.0 mmol/L <2.0 – ≥1.75 mmol/L <1.75 – ≥ 1.5 mmol/L <1.5 mmol/L	CTCAE grade 1-4
Magnesium	Hypermagnesemia >ULN - ≤ 1.23 mmol/L >1.23 – ≤ 3.30 mmol/L >3.30 mmol/L	CTCAE grade 1, 3, 4 No CTCAE grade 2
	Hypomagnesemia <LLN - ≥ 0.5 mmol/L <0.5 – ≥ 0.4 mmol/L <0.4 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
Inorganic phosphate	Hypophosphatemia <0.74 – ≥ 0.6mmol/L <0.6 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
ALT	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN >5 – ≤ 8 xULN >8 – ≤ 20.0 xULN >20.0 x ULN	Per FDA DILI Guidance Jul 2009 and CTCAE
AST	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN	FDA DILI Guidance and CTCAE

	>5 – ≤ 8 xULN >8 – ≤ 20.0 xULN >20.0 x ULN	
ALT or AST	(ALT>ULN and ALT ≤ 3 xULN) or (AST>ULN and AST≤ 3 xULN) (ALT>3 xULN and ALT ≤ 5 xULN) or (AST>3xULN and AST≤ 5 xULN) (ALT>5 xULN and ALT ≤ 8 xULN) or (AST>5xULN and AST≤ 8 xULN) (ALT>8 xULN and ALT ≤ 20 xULN) or (AST>8xULN and AST≤ 20 xULN) ALT>20 xULN or AST> 20 xULN	FDA DILI Guidance
Alkaline Phosphatase	>ULN - ≤ 1.5xULN >1.5 – ≤ 2.5 xULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	FDA DILI Guidance and CTCAE
Total Bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	FDA DILI Guidance and CTCAE
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	FDA DILI Guidance Jul 2009
Hematology		
WBC	WBC decreased <LLN - ≥ 3.0 x 10e9 /L <3.0 – ≥ 2.0 x 10e9 /L <2.0 – ≥ 1.0 x 10e9 /L <1.0 x 10e9 /L	CTCAE grade 1-4
	Leukocytosis >100 x 10e9 /L	CTCAE grade 3 (only Grade available)
Lymphocytes	Lymphocyte decreased <LLN - ≥ 0.8 x10e9 /L <0.8 – ≥ 0.5 x10e9 /L <0.5 – ≥ 0.2 x10e9 /L <0.2 x10e9 /L	CTCAE grade 1-4
	Lymphocyte increased >4 – ≤ 20 x10e9/L >20 x10e9/L	CTCAE grade 2, 3 (only Grades available)
Neutrophils	Neutrophil decreased <LLN - ≥ 1.5 x10e9 /L <1.5 – ≥ 1.0 x10e9 /L <1.0 – ≥ 0.5 x10e9 /L <0.5 x10e9 /L	CTCAE grade 1-4
Hemoglobin	Hgb decreased (anemia) <LLN - ≥ 100 g/L <100 – ≥ 80 g/L < 80 g/L	CTCAE grade 1-3

	Hgb increased >ULN - ≤ 20 g/L above ULN >20 g/L above ULN - ≤ 40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3
Platelets	Platelet decreased <LLN - ≥ 75.0 x 10e9 /L <75.0 – ≥ 50.0 x 10e9 /L <50.0 – ≥ 25.0 x 10e9 /L <25.0 x 10e9 /L	CTCAE grade 1-4

Table 11-7 Threshold Criteria for Coagulation

Parameter	Criteria	Comments
Activated partial thromboplastin time (PTT)	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN	CTCAE grade 1-3

Table 11-8 Threshold Criteria for ECGs

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

Table 11-9 Threshold Criteria for Vital Signs

Parameter	Threshold Criteria	Comments
HR	Same PCS as above in ECG category	
SBP	SBP increased	809/770 analyses
	>140 mmHg	
	>160 mmHg	
	>10 mmHg increase from baseline	
	>20 mmHg increase from baseline	
	>140 mmHg & >10 mmHg increase from baseline	
	>140 mmHg & >20 mmHg increase from baseline	
	>160 mmHg & >10 mmHg increase from baseline	
	>160 mmHg & >20 mmHg increase from baseline	
	SBP decrease	Per HV grade 1, 3, plus shift change
	<90 mmHg	
	<80 mmHg	
	>10 mmHg decrease from baseline	
	>20 mmHg decrease from baseline	
	<90 mmHg and >10 mmHg decrease from baseline	
	<90 mmHg and >20 mmHg decrease from baseline	
	<80 mmHg and >10 mmHg decrease from baseline	
	<80 mmHg and >20 mmHg decrease from baseline	
DBP	DBP increased	809/770 analyses
	>90 mmHg	
	>100 mmHg	
	>5 mmHg increase from baseline	
	>10 mmHg increase from baseline	
	>90 mmHg and >5 mmHg increase from baseline	
	>90 mmHg and >10 mmHg increase from baseline	
	>100 mmHg and >5 mmHg increase from baseline	
	>100 mmHg and >10 mmHg increase from baseline	
	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