VERTEX

*VERTEX PHARMACEUTICALS INCORPORATED*

# Statistical Analysis Plan

## Protocol Number VX15-809-112

**A Phase 4, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Study of the Effect of Lumacaftor/Ivacaftor Combination Therapy on Exercise Tolerance in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation**

**Author of SAP:** [redacted]

**Version: 1.0**

**Version Date of SAP: 17 May 2017**

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210-1862

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# 1 TABLE OF CONTENTS

[redacted]



[redacted]



[redacted]



[redacted]



[redacted]

## List of Tables

# 2 LIST OF ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| AE | adverse event |
| ALP | alkaline aminotransferase |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| AR(1) | autoregressive model of order 1 |
| AST | aspartate aminotransferase |
| AT | Anaerobic threshold |
| BMI | body mass index ($kg/m^2$) |
| bpm | beats per minute |
| CF | cystic fibrosis |
| CFQ-R | Cystic Fibrosis Questionnaire – Revised |
| CFTR | cystic fibrosis transmembrane conductance regulator |
| CI | confidence interval |
| CMH | Cochran-Mantel-Haenszel |
| CPET | Cardiopulmonary exercise testing |
| CRF | case report form |
| CRO | contract research organization |
| [redacted] | |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| FAS | full analysis set |
| $FEF_{25-75\%}$ | forced expiratory flow, midexpiratory phase |
| $FEV_1$ | forced expiratory volume in 1 second |
| FVC | forced vital capacity |
| *F508del* | *CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein |
| GAD-7 | Generalized Anxiety Disorder |
| $HNV_{FEV}$ | Hankinson predicted value of $FEV_1$ (L) |
| $HNV_{FEF25-75\%}$ | Hankinson predicted value of $FEF_{25-75\%}$ (L/sec) |
| $HNV_{FVC}$ | Hankinson predicted value of FVC (L) |
| ISE | integrated summary of efficacy |
| LFT | liver function test |
| LOCF | last observation carried forward |
| M1 | VRT-837018, hydroxymethyl-ivacaftor, metabolite of ivacaftor |
| M6 | VRT-842917, carboxy-ivacaftor, ivacaftor acid, metabolite of ivacaftor |
| MH | Mantel-Haenszel |
| max | maximum value |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | multiple imputation |
| min | minimum value |
| MMRM | mixed model repeated measure |
| N | number of subjects |

| Abbreviation | Term |
|---|---|
| [redacted] | |
| PD | pharmacodynamic/pharmacodynamics |
| PHQ-8 | Patient Health Questionnaire |
| PK | pharmacokinetic/pharmacokinetics |
| PPS | per protocol set |
| PT | preferred term |
| q12h | every 12 hours |
| QRS | Q, R, and S-wave define the QRS-complex in an ECG |
| QT | QT interval: The duration of ventricular depolarization and subsequent repolarization; it is measured from the beginning of the QRS complex to the end of the T wave |
| QTc | QT interval corrected for heart rate |
| QTcF | QT interval corrected for heart rate with Fridericia's correction |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SE | standard error |
| SI | System International |
| SOC | system organ class |
| TEAE | treatment-emergent adverse event |
| TSQM | Treatment Satisfaction Questionnaire for Medication |
| ULN | upper limit of normal |
| $VCO_2$ | Carbon dioxide production |
| $VO_2$ | Oxygen consumption |
| $VO_2$max | Maximal Oxygen consumption |
| $WNV_{FEV}$ | Wang predicted value of $FEV_1$ (L) |
| $WNV_{FEF25-75\%}$ | Wang predicted value of $FEF_{25-75\%}$ (L/sec) |
| $WNV_{FVC}$ | Wang predicted value of FVC (L) |
| WHODDE | World Health Organization Drug Dictionary Enhanced |

# 3 SUMMARY OF MODIFICATIONS

No applicable as of 01 August 2016

# 4 INTRODUCTION

This SAP describes the planned final analyses for the Study VX15-809-112 data and is based on the

- approved clinical study protocol (Version 1.0, dated 15 January 2016),
- approved electronic case report form (eCRF) (dated 13 January 2017).

Study VX15-809-112 is a Phase 4, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Study of the Effect of Lumacaftor/Ivacaftor Combination Therapy on Exercise Tolerance in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation.

This SAP (Methods) documents the planned final statistical analyses of efficacy and safety introduced in the study protocol of VX15-809-112, and describes the corresponding data presentations. It also documents additional efficacy and safety analyses not specified in the protocol, which will provide supportive information to the scientific understanding of the drug entity.

The [redacted] Biostatistics Department will perform the statistical analysis of the efficacy and safety data under the supervision of Vertex Biometrics Department; SAS (Version 9.2, or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the final clinical data lock and treatment unblinding for the study.

# 5 STUDY OBJECTIVES

## 5.1 Primary Objective

To evaluate the effect of LUM/IVA on exercise tolerance in subjects with CF, homozygous for the *F508del-CFTR* mutation

## 5.2 Secondary Objectives

To evaluate the effect of LUM/IVA on manifestations of CF affected by exercise tolerance and training

# 6 STUDY ENDPOINTS

## 6.1 Efficacy Endpoints

### 6.1.1 Primary Endpoint

Relative change from baseline in $VO_2$max during cardiopulmonary exercise testing (CPET) at Week 24

### 6.1.2 Secondary Endpoints

**Key Secondary Endpoint**

- Relative change from baseline in exercise duration during CPET at Week 24

**Other Secondary Endpoints**

- Absolute change from baseline in exercise duration during CPET at Week 24
- Absolute change from baseline in $VO_2$max during cardiopulmonary exercise testing (CPET) at Week 24
- Absolute and relative change from baseline in oxygen consumption ($VO_2$) at anaerobic threshold (AT) (the point during exercise at which lactate starts to accumulate) at Week 24
- Absolute and relative change from baseline in functional $VO_2$ gain at Week 24
- Absolute and relative change from baseline in the slope of pulmonary ventilation (VE) versus carbon dioxide production ($VCO_2$) at Week 24
- Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at Week 24
- Relative change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at Week 24
- Absolute change from baseline in body mass index (BMI) at Week 24
- Relative change from baseline in body mass index (BMI) at week 24
- Absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score at Week 24
- Absolute change from baseline in overall Patient Health Questionnaire (PHQ-8) and Generalized Anxiety Disorder (GAD-7) scores at Week 24
- Absolute change from baseline in total daily physical activity as determined by actigraphy at Week 24
- Relative change from baseline in total daily physical activity as determined by actigraphy at Week 24
- Absolute change from baseline in duration of sleep time during the night at Week 24

- Relative change from baseline in duration of sleep time during the night at Week 24
- Absolute change from baseline in time above sedentary duration at Week 24
- Relative change from baseline in time above sedentary duration at Week 24

[redacted]

## 6.2 Safety Endpoints

The safety endpoints are as follows:

- Adverse events
- Clinical laboratory
- Vital signs
- Pulse oximetry
- Physical examination
- Ophthalmologic findings (for subjects under 18 years of age only)

## 6.3 Pharmacokinetic Endpoints

Not applicable

# 7 STUDY DESIGN

## 7.1 Overall Design

This is a Phase 4, randomized, double-blind, placebo-controlled, parallel-group study in subjects aged 12 years and older with CF who are homozygous for the *F508del-CFTR* mutation. This study is designed to evaluate the effect of LUM/IVA on exercise tolerance.

The study includes a Screening Period, a Treatment Period, and a Safety Follow-up Visit. Approximately 66 subjects will be randomized 1:1 (LUM/IVA: placebo) to the treatment arms shown in Figure 7-1 and stratified by $ppFEV_1$ at baseline (<70% and ≥70% predicted). Subjects will receive study drug (LUM/IVA or placebo) for 24 weeks, in addition to their current CF medication regimen. They will return to the study center 4 weeks after their last dose of study drug for the Safety Follow-up Visit. It is recommended that subjects remain on

a stable CF medication regimen from 4 weeks before Day 1 through the Safety Follow-up Visit.

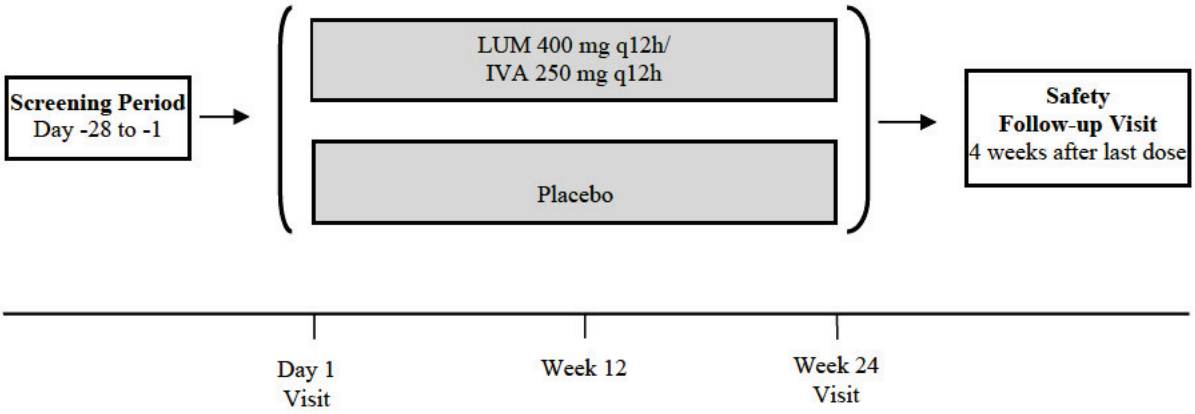
Subjects will be reminded of the standard exercise recommendations for patients with CF, and their daily activity will be tracked using an actigraphy device.

[redacted]

**About Cardiopulmonary exercise testing (CPET)**

CPET will be performed at the time points noted in study schedule. CPET will be conducted using the Godfrey protocol[1], which has been used in a number of studies of exercise tolerance in patients with CF. According to the Godfrey protocol, CPET will be conducted using a cycle that ramps resistance over time. Pulse oximetry is utilized during CPET.

**Figure 7-1 Schematic View of the Study Design**




## 7.2 Sample Size and Power

Assuming a common standard deviation (SD) of 10% for the primary efficacy endpoint and a dropout rate of 10%, a sample size of 33 subjects in each treatment group would provide at least 80% power to detect a difference of 7.5% between the means for the 2 treatment groups using a 2-sided test at the 0.05 significance level. If the true difference is smaller, or if there

is greater variability, a larger sample size would be required to provide 80% power. Table 7-1 shows the required sample sizes for various assumptions about the true treatment effect using a 2-sided test at the 0.05 significance level.

Because LUM/IVA has recently been approved in several countries, additional data independent of this study may emerge while this study is underway, which would allow a more precise estimation of the true treatment effect. The final sample size may be recalculated based on these data, and the protocol may be amended as appropriate.

**Table 7-1 Sample Sizes for 80% Power**

| True Difference Between Placebo and LUM/IVA Effects on Primary Endpoint | Sample Size Needed for 80% Power (subjects per treatment group) |
|---|---|
| 5.0% | 72 |
| 5.5% | 59 |
| 6.0% | 50 |
| 6.5% | 44 |
| 7.0% | 38 |
| 7.5% | 33 |

## 7.3 Randomization

A total of approximately 66 subjects (33 per arm) who meet eligibility criteria will be stratified by age (<18 versus ≥18 years of age), sex (male versus female), and percent predicted $FEV_1$ severity determined at the baseline Visit (<70 versus ≥70), and then randomized (1:1) to 1 of the 2 treatment arms.

The randomization codes were produced by a designated vendor [redacted]. In order to protect the study blind and maintain the scientific integrity of the data, 1 Vertex biostatistician and 1 [redacted] biostatistician were involved in the randomization process for each study: a Vertex biostatistician who is blinded to the actual treatment code and a [redacted] unblinded biostatistician who is not associated with the study. Below is a brief description of the randomization process.

- The Vertex biostatistician created the randomization specification.
- The external designated vendor [redacted] created the dummy randomization code, which was reviewed and approved by the Vertex biostatistician.
- After approval, the external designated vendor generated the production randomization list and provided it to the unblinded [redacted] biostatistician for review.
- After all outstanding issues were resolved; the external designated vendor generated the final randomization list and provided it to the unblinded [redacted] biostatistician to upload in the designated final randomization study area.

The unblinded [redacted] biostatistician provided the final randomization list to the interactive web response system (IWRS) vendor. A copy of the final randomization list, provided in sealed tamper-evident envelopes, was archived at Vertex.

## 7.4 Blinding and Unblinding

### 7.4.1 Blinding

All subjects, site personnel including the investigator, the site monitor, and the Vertex study team will be blinded for the duration of the study, 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 their 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 Clinical Operations IWRS management
- Vertex Clinical Supply Chain
- DMC
- Vertex medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time

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.

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.

### 7.4.2 Unblinding

Unblinding of the individual subject's treatment by the investigator should be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. Details are provided in the clinical study protocol Section 11.12.2.

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the Vertex medical monitor should be notified within 24 hours of the unblinding event. The reason and the date of the unblinding should be documented clearly in the subject's source documents. Information regarding the treatment assignment obtained

from the unblinding should be maintained in a secure location with controlled access and must not be shared with Vertex, contract research organizations (CROs), or any site personnel (other than the physician treating the subject). In addition, the investigator should consider whether the clinical event that prompted unblinding should be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS, per corresponding section of the clinical study protocol.

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

# 8 ANALYSIS SETS

Assignment of subjects to analysis sets will be done prior to clinical data lock for the study.

The following analysis sets will be defined: All Subjects Set, Full Analysis Set (FAS) and Safety Set.

The All Subjects Set will be defined as all subjects in the study who were randomized or dosed (received any amount of study drug). All subject data listings will be use the All Subjects Set, unless otherwise specified.

## 8.1 Efficacy Sets

### 8.1.1 Full Analysis Set (FAS)

The FAS will include all randomized subjects who received any amount of study drug. The treatment assignment for the FAS will be as randomized. The FAS will be used for all efficacy analyses.

## 8.2 Safety Set

The Safety Set will include all subjects who received any amount of study drug. The treatment assignment for the Safety Set will be as treated. All safety analyses will be conducted using the Safety Set.

## 8.3 Other Analysis Set

Not applicable.

# 9 STATISTICAL ANALYSIS

## 9.1 General Considerations

The Schedule of Assessments is provided in Appendix A.

All individual subject data for those randomized or exposed to 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, standard error (SE), standard deviation (SD), median, minimum value (min), and maximum value (max). The precision of the measurement for each continuous variable will be used to determine the number of decimal places to present in tables, figures, and derived listings. Minimum and maximum values will be reported with the same precision as the units of measure. The mean and median will be reported to 1 greater decimal place, and the SE and SD will be reported to 2 additional decimal places. Any values that require transformation to standard units (metric or SI) will be converted with the appropriate corresponding precision.

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

**Baseline Value:** Unless otherwise specified, the baseline value will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the initial administration of study drug. Baseline CPET data will be collected on Day 1 prior to the initial administration of study drug. Unscheduled visit measurements will be included for derivation of baseline. For actigraphy variables, baseline data will be defined as the mean of the data collected for the 7 days immediately preceding Day 1 (Day -7 to Day -1) during the Screening Period.

**Absolute Change from baseline** will be calculated as Post baseline value - Baseline value.

**Relative change from baseline** will be calculated and expressed in percentages as 100× (Post baseline value - Baseline value)/Baseline value.

**Unscheduled Visits:** Unscheduled visit measurements will be included in listings, for derivation of visit windows and computation of baseline/last on-treatment visit, and for the analysis of maximum/minimum on-treatment values and maximum/minimum changes from baseline values.

**Visit Windows:** Appendix C defines the visit window mapping rules to derive the analysis visits.

Repeated observations within the same visits window

- For all efficacy parameters, if there are multiple measurements within a visit window, the record at the scheduled visit will be used. If there are no measurements at the scheduled visit, then 1) the record closest to the target day will be used; or 2) if there are multiple records with the same distance to the target day, the latest record will be used.
- For all safety parameters, if there are multiple measurements within a visit window, then 1) the record closest to the target day will be used; or 2) if there are multiple records with the same distance to the target day, the latest record will be used.

BMI will follow visit window rules for efficacy parameters when being considered as an efficacy endpoint.

**Incomplete/Missing data** will not be imputed, unless otherwise specified; i.e., all missing values will remain as missing in all statistical analyses and listings, unless otherwise specified. Missing post-baseline values will not be imputed for efficacy analysis conducted

using a mixed model for repeated measures (MMRM) approach, which makes use of all available data even if a subject has missing data at some post-baseline visits.

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

**Repeated Observations:** Measurements recorded at different time points are defined as repeated observations. If an assessment has planned repeated measurements, then statistical summaries will present all planned time points, as appropriate.

## 9.2 Background Characteristics

### 9.2.1 Subject Disposition

The number of subjects in the following analyses sets will be summarized:

- All Subjects Set
- Randomized
- FAS (randomized and dosed)
- Safety Set

The number and percentage of subjects in each disposition category will be summarized with the number in the FAS as the denominator, together with the number of subjects randomized but never dosed:

- Randomized but never dosed (only showing number of subjects)
- Completed treatment
- Prematurely discontinued treatment and the reasons for discontinuations
- Last completed on-treatment scheduled visit for subjects who discontinued treatment
- Completed study
- Prematurely discontinued the study and the reasons for discontinuations

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

### 9.2.2 Demographics and Baseline Characteristics

Demographic data will be summarized based on the FAS:

- Age
- Age groups (< 18 and ≥18 years)
- Sex (female and male)
- Ethnicity

- Race

Baseline characteristics will be summarized based on the FAS:

- Weight (kg)
- Weight z-score (subjects ≤20 years old) Weight, adjusted for age and sex, will be analyzed as weight-for-age z-score (weight z-score). The calculation of weight z-score is similar to that of BMI z-score (using the CDC growth charts and the derivation described). Using the same equation as in the CDC growth charts and the derivation described in the website below, *X* in the equation is the collected weight and *L*, *M*, and *S* parameters are selected from the CDC weight-for-age chart. The WTAGE file contains these parameters by sex and age; it is available at the website http://www.cdc.gov/growthcharts/percentile_data_files.htm. NOTE: The CDC growth charts are designed for use in pediatric populations (2 to 20 years of age); therefore, weight z-score will be calculated only for subjects in this age range.
- Height (cm)
- Height z-score (subjects ≤20 years old) Height, adjusted for age and sex, will be referred to as height-for-age z-score (or height z-score). The calculation of height z-score is similar to that of BMI z-score (using the CDC growth charts and the derivation described). Using the same equation as in the CDC growth charts and the derivation described in the website below, *X* in the equation is the collected height and *L*, *M*, and *S* parameters are selected from the CDC height-for-age chart. The STATAGE file contains these parameters by sex and age; it is available at the website http://www.cdc.gov/growthcharts/percentile_data_files.htm. NOTE: The CDC growth charts are designed for use in pediatric populations (2 to 20 years of age); therefore, height z-score will be calculated only for subjects in this age range.
- BMI ($kg/m^2$)
- BMI z-score (subjects ≤20 years old)
- Percent predicted $FEV_1$ at screening (<70, ≥70)
- Percent predicted $FEV_1$ at baseline (<40, ≥40 to <70, ≥70 to ≤90, >90)
- Percent predicted $FEV_1$ at baseline
- $FEV_1$ (L)
- FVC (L)
- Percent predicted FVC
- $FEF_{25-75\%}$ (L/sec)
- Percent predicted $FEF_{25-75\%}$
- $FEV_1$/FVC
- $VO_2$max
- Exercise duration during CPET

- Oxygen consumption ($VO_2$) at anaerobic threshold (AT) (the point during exercise at which lactate starts to accumulate)
- Functional $VO_2$ gain
- Slope of pulmonary ventilation (VE) vs. carbon dioxide production ($VCO_2$)
- Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score
- Overall Patient Health Questionnaire (PHQ-8) score
- Generalized Anxiety Disorder (GAD-7) score
- Physical activity as determined by actigraphy
- Duration of sleep time during the night

[redacted]

- Received dornase alfa before first dose of study drug (Yes, No)
- Received any inhaled antibiotic before first dose of study drug (Yes, No)
- Received any bronchodilator before first dose of study drug (Yes, No) Note: On the Prior and Concomitant Medications page, only those coded as bronchodilator will be included.
- Received any inhaled bronchodilator before first dose of study drug (Yes, No) Note: On the Prior and Concomitant Medications page, only those coded as bronchodilator will be included.
- Received any inhaled bronchodilator before first dose of study drug (Short-Acting Only, vs (Short-Acting and Long-Acting) or Long-Acting only, vs No)
- Received any inhaled hypertonic saline before first dose of study drug (Yes, No)
- Received any inhaled corticosteroids before first dose of study drug (Yes, No)

Medical history summary will be presented for the FAS.

The important protocol deviation programming rules (based on the clinical database) are provided in Appendix G. Important protocol violations/deviations (based on the clinical database or from the site deviation log) will be summarized descriptively based on the FAS. Important protocol deviations/violations will be provided as a subject data listing.

### 9.2.3 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:** medication started before initial dosing of study drug, regardless of when it ended.
- **Concomitant medication:** medication continued or newly received at or after initial dosing of study drug to 28 days after the last dose of study drug.
- **Post-treatment medication:** medication continued or newly received after 28 days after the last dose of study drug.

A given medication can be classified as a prior medication, a concomitant medication, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment. If a medication has a missing or partially missing start/end date or time and it cannot be determined whether it was taken before initial dosing, concomitantly, or more than 28 days after the last dose of study drug, it will be considered as prior, concomitant, and post-treatment.

Prior medications and concomitant medications will be summarized descriptively by preferred term (PT) based on the FAS. Prior medications and concomitant medications with a frequency of ≥5% at the PT level in any treatment group will be summarized descriptively by PT. Post-treatment medications will be listed for each subject.

In addition, to evaluate whether the medications have stable use after receiving study drug, shifts from use prior to the first dose (Yes, No) to use during the treatment-emergent period (chronic versus intermittent) will be summarized using number of subjects and percentages for the following medication categories:

- Inhaled antibiotics
- Inhaled bronchodilator
- Inhaled hypertonic saline
- Inhaled corticosteroids

A medication is considered to be used chronically during the treatment-emergent period if it is used on ≥ 25% of days during the treatment-emergent period; and is considered to be used intermittently during the treatment-emergent period if it is used on <25% of days during the treatment-emergent period. The treatment-emergent period is the period at or after the initial dosing of study drug to 28 days after the last dose of study drug.

As an intermediate step for programming purposes, medications with missing or partially missing start dates will have 2000 imputed for the missing year, January for the missing month, and 1 for the missing day; medications with missing or partially missing stop dates will have 2050 imputed for the missing year, December for the missing month, and the last day of the month for the missing day. The logic to decide the category of a medication is presented in Table 9-1:

**Table 9-1 Logic for Determining the Category of a Medication**

| | Medication end date | | |
|---|---|---|---|
| **Medication start date** | < first dose date of | ≥ first dose date and | > last dose date + 28 |

| | study drug | ≤ last dose date +28 days | days |
|---|---|---|---|
| < first dose date of study drug | P | PC | PCA |
| ≥ first dose date and ≤ last dose date + 28 days | - | C | CA |
| > last dose date + 28 days | - | - | A |

P: Prior; C: Concomitant; A: Post

### 9.2.4 Study Drug Exposure

Duration of study drug exposure is defined as: last dose date – first dose date + 1 day, regardless of any interruptions in dosing. If the last dose date of study drug is missing, the subject's discontinuation or completion date will be used for analysis purpose.

Duration of study drug exposure will be summarized descriptively as quantitative variables (number, mean, SE, SD, median, minimum [min], and maximum [max]). Additionally, the total duration of study drug exposure, defined as the sum of the subject's duration of treatment exposure and expressed in patient years, will be provided.

Exposure summaries will be based on the FAS.

### 9.2.5 Study Drug Compliance

Study drug compliance will be calculated as follows:

$$100 \times [1 - (\text{Total number of days study drug interrupted}) / (\text{Duration of study drug exposure})].$$

The total number of days of study drug interrupted is defined as the sum of (number of days of study drug interrupted in each interval), where number of days of study drug interrupted in each interval is defined as the interruption end date - the corresponding interruption start date + 1.

In calculating the total number of days study drug interrupted, only interruptions with duration of ≥3 days will be considered. An interruption with duration of < 3 days will not be considered in the calculation.

Treatment compliance percentages will be summarized descriptively as quantitative variables (number, mean, SE, SD, median, min, and max). The n and percentage of subjects whose compliance is <80% or ≥80% will be summarized.

A list of subjects with <80% compliance will be provided.

Study drug compliance will be summarized based on the FAS.

## 9.3 Efficacy Analysis

Unless otherwise defined, all efficacy analyses described in this section will include all measurements up to Week 24 [inclusive], both on-treatment measurements and measurements after treatment discontinuation.

### 9.3.1 Analysis of Primary Efficacy Endpoint

#### 9.3.1.1 Definition of Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage change from baseline in $VO_2$max (mL/kg/min [milliliter per kilogram per minute]) during cardiopulmonary exercise testing (CPET) at Week 24, defined as $VO_2$max (mL/kg/min) during cardiopulmonary exercise testing (CPET) at Week 24 minus $VO_2$max (mL/kg/min) during cardiopulmonary exercise testing (CPET) at baseline, divided by $VO_2$max (mL/kg/min) during cardiopulmonary exercise testing (CPET) at baseline.

$VO_2$max is the largest $VO_2$ value during exercise.

$VO_2$max is found in the column(s) with a heading of $VO_2$ in the 20-second averaged CPET spreadsheets.

Some spreadsheets have a column reporting $VO_2$ in units of mL/min or L/min only, while others have an additional column reporting $VO_2$ as weight-based units with a designation of kg in the column header. The header title may vary, but when the term kg appears in the header, the actual units are mL/kg/min.

If the $VO_2$ is reported in L/min, it will need to be converted to achieve final reported units of mL/kg/min (1L=1000mL).

If there is no weight-based column showing kg (i.e., $VO_2$ is reported only in mL/min or L/min), the weight in kg will need to be pulled from the eCRF in order to convert these values to mL/kg/min.

#### 9.3.1.2 Primary Analysis of Primary Efficacy Endpoint

The primary analysis for the primary efficacy endpoint will be based on a mixed model repeated measures (MMRM) using SAS PROC MIXED based on the FAS.

The model, including percentage change from baseline in $VO_2$max (including all measurements up to Week 24 [inclusive], both on-treatment measurements and measurements after treatment discontinuation) as the dependent variable, treatment, visit, and treatment-by-visit interaction as fixed effects, with adjustment for sex (male versus female), age group at baseline (<18 versus ≥18 years old), percent predicted $FEV_1$ at baseline (<70

versus ≥70), baseline $VO_2$max value and subject as a random effect will be used to test the difference between active treatment group versus placebo. The primary result obtained from the model will be the treatment effect at Week 24.

Descriptive summary statistics including number of subjects, mean, standard error, and least-square means (LS means) along with the *P* values will be provided. In particular, the difference in LS means as well as LS means within each group and the corresponding 95% CI will be provided along with the *P* values to assess the treatment difference between placebo and lumacaftor in combination with ivacaftor. Additionally, the *P* value testing the treatment-by-visit interaction will be provided to assess the consistency of treatment effect over different visits.

The repeated-measures analysis will be based on the restricted maximum likelihood method assuming an unstructured covariance structure to model the within-subject errors. A Kenward-Roger approximation will be used for the denominator degrees of freedom. If there is a convergence problem due to the unstructured covariance matrix, a compound symmetry covariance structure will be used to model the within-subject errors. With a mixed effects model as the primary analysis model based on restricted maximum likelihood estimation and assuming that conditional on fixed and random effects, data are missing at random, no imputation of missing data will be done.

In addition, raw values of percentage change from baseline in $VO_2$max at Week 24, and raw values of percentage change from baseline in $VO_2$max at Week 12 will be summarized descriptively (number, mean, SE, SD, median, min, and max).

[redacted]

[redacted]

### 9.3.2 Analysis of Secondary Efficacy Endpoints

**Key Secondary Endpoint**

- Relative change from baseline in exercise duration during CPET at Week 24

**Other Secondary Endpoints**

- Absolute change from baseline in exercise duration during CPET at Week 24
- Absolute change from baseline in $VO_2$max during cardiopulmonary exercise testing (CPET) at Week 24
- Absolute and relative change from baseline in oxygen consumption ($VO_2$) at anaerobic threshold (AT) (the point during exercise at which lactate starts to accumulate) at Week 24
- Absolute and relative change from baseline in functional $VO_2$ gain at Week 24
- Absolute and relative change from baseline in the slope of pulmonary ventilation (VE) versus carbon dioxide production ($VCO_2$) at Week 24
- Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at Week 24
- Relative change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at Week 24
- Absolute change from baseline in body mass index (BMI) at Week 24
- Relative change from baseline in body mass index (BMI) at week 24
- Absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score at Week 24
- Absolute change from baseline in overall Patient Health Questionnaire (PHQ-8) and Generalized Anxiety Disorder (GAD-7) scores at Week 24
- Absolute change from baseline in total daily physical activity as determined by actigraphy at Week 24

- Relative change from baseline in total daily physical activity as determined by actigraphy at Week 24
- Absolute change from baseline in duration of sleep time during the night at Week 24
- Relative change from baseline in duration of sleep time during the night at Week 24
- Absolute change from baseline in time above sedentary duration at Week 24
- Relative change from baseline in time above sedentary duration at Week 24

[redacted]

#### 9.3.2.1 Definition of Secondary Efficacy Endpoints

##### 9.3.2.1.1 Definition of Key Secondary Efficacy Endpoints

**Relative change from baseline in exercise duration during CPET at Week 24**

Relative change from baseline in exercise duration measured in the unit of seconds during CPET at Week 24 is the key secondary efficacy endpoint, defined as exercise duration measured in the unit of seconds during CPET at Week 24 minus exercise duration measured in the unit of seconds during CPET at baseline, divided by exercise duration measured in the unit of seconds during CPET at baseline.

Exercise duration is defined as the time at the termination of CPET exercise minus the corresponding time when CPET starts for each CPET exercise.

##### 9.3.2.1.2 Definition of Additional Secondary Efficacy Endpoints

**Absolute change from baseline in exercise duration during CPET at Week 24**

Defined as exercise duration measured in the unit of seconds during CPET at Week 24 minus exercise duration measured in the unit of seconds during CPET at baseline

**Absolute change from baseline in $VO_2$max (mL/kg/min) during cardiopulmonary exercise testing (CPET) at Week 24**

Defined as $VO_2$max (mL/kg/min) during cardiopulmonary exercise testing (CPET) at Week 24 minus $VO_2$max (mL/kg/min) during cardiopulmonary exercise testing (CPET) at baseline

**Absolute change from baseline in oxygen consumption ($VO_2$) (mL/min) at anaerobic threshold (AT) (the point during exercise at which lactate starts to accumulate) at Week 24**

Defined as oxygen consumption ($VO_2$) (mL/min) at AT at Week 24 minus oxygen consumption ($VO_2$) (mL/min) at AT at baseline.

**Relative change from baseline in oxygen consumption ($VO_2$) (mL/min) at anaerobic threshold (AT) (the point during exercise at which lactate starts to accumulate) at Week 24**

Defined as oxygen consumption ($VO_2$) (mL/min) at AT at Week 24 minus oxygen consumption ($VO_2$) (mL/min) at AT at baseline, divided by oxygen consumption ($VO_2$) (mL/min) at AT at baseline

Before reviewing the results for $VO_2$ at the time that AT occurred, it must first be determined if the appropriate number of overreaders input this value into the eCRF. There are separate eCRF entries for the time at AT and the actual $VO_2$ value at the time of AT. However, each of these fields should have the identical number of entries, either 2 or 3. If they do not, no further evaluation of these parameters should be carried out, and Vertex must be notified. If they do, please proceed.

The time of AT is reported in the eCRF by either 2 or 3 independent overreaders. The final, averaged time at AT will be determined following the guidelines:

- If the time at AT results is available from two overreaders, the absolute difference between these results (in seconds) will be divided by the lower of the two results (in seconds) to determine if the readings are within 5% ($\leqslant$5%) of each other. If they are, the average value of the two readings will be used as the final time at AT. If the results are not within 5% of each other, no further evaluation of this parameter should be carried out, and Vertex must be notified.
- If time at AT results is available from 3 overreaders, the absolute difference between the highest and lowest of the 3 results (in seconds) will be divided by the lowest of the results (in seconds) to determine if these readings are within 7% ($\leq$7%) of each other. If they are, the average value of all three readings will be used as the final time at AT. If their results are not within 7% of each other, no further evaluation of this parameter should be carried out, and Vertex must be notified.

Once it has been confirmed that the appropriate number of overreaders have input their values, the average of these 2 or 3 $VO_2$ values in the eCRF will be reported as the final $VO_2$ at the time of AT.

**Absolute change from baseline in functional $VO_2$ gain at Week 24**

Defined as functional $VO_2$ gain at Week 24 minus functional $VO_2$ gain at baseline.

**Relative change from baseline in functional $VO_2$ gain at Week 24**

Defined as functional $VO_2$ gain at Week 24 minus functional $VO_2$ gain at baseline, divided by functional $VO_2$ gain at baseline.

Functional $VO_2$ gain is calculated as $\Delta VO_2$/Max Watts.
This data is derived from the 20-second averaged CPET spreadsheets.

- $\Delta$ $VO_2$ = Final $VO_2$ – Rest $VO_2$
  - Final $VO_2$ (ml/min) is the mean of the last 3 available values of $VO_2$ at the end of exercise
  - Rest $VO_2$ (ml/min) is the mean of the last 3 available values of $VO_2$ immediately before the start of exercise
- Maximum Watts achieved during exercise can be found in the WR, Work, or Watts column on the 20-sec averaged CPET spreadsheets.

If $VO_2$ reported in L/min, this will need to be converted to mL/min before applying the formulas above (1L=1000mL).

**Absolute change from baseline in the slope of pulmonary ventilation (VE, L/min) versus carbon dioxide production ($VCO_2$, L/min) at Week 24**

Defined as the slope of pulmonary ventilation (VE, L/min) versus carbon dioxide production ($VCO_2$, L/min) at Week 24 minus the slope of pulmonary ventilation (VE, L/min) versus carbon dioxide production ($VCO_2$, L/min) at baseline

**Relative change from baseline in the slope of pulmonary ventilation (VE, L/min) versus carbon dioxide production ($VCO_2$, L/min) at Week 24**

Defined as the slope of pulmonary ventilation (VE, L/min) versus carbon dioxide production ($VCO_2$, L/min) at Week 24 minus the slope of pulmonary ventilation (VE, L/min) versus carbon dioxide production ($VCO_2$, L/min) at baseline, divided by the slope of pulmonary ventilation (VE, L/min) versus carbon dioxide production ($VCO_2$, L/min) at baseline

This data is derived from the breath-by-breath CPET spreadsheets.

VE and $VCO_2$ data will be measured from the beginning to the end of exercise during each corresponding CPET session.

A linear regression model using pulmonary ventilation (VE, L/min) as the dependent variable and carbon dioxide production ($VCO_2$, L/min) as the covariate without an intercept will be used to derive the slope estimate from the breath by breath data.

**Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at Week 24**

Defined as percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at Week 24 minus percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at baseline (Please see appendix D for the definition of $ppFEV_1$)

**Relative change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at Week 24**

Defined as percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at Week 24 minus percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at baseline, divided by percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at baseline (Please see appendix D for the definition of $ppFEV_1$)

**Absolute change from baseline in body mass index (BMI) raw score at Week 24**

Defined as body mass index (BMI) raw score at Week 24 minus body mass index (BMI) raw score at baseline

**Relative change from baseline in body mass index (BMI) raw score at Week 24**

Defined as body mass index (BMI) raw score at Week 24 minus body mass index (BMI) raw score at baseline, divided by body mass index (BMI) raw score at baseline

BMI will be calculated as the following:

$$BMI = \text{Weight (kg)}/(\text{height (m)}^2)$$

**Absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score at Week 24**

Defined as Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score at Week 24 minus Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score at baseline

The CFQ-R[2,3,4] is a validated CF-specific instrument that measures quality-of-life domains. There are three different versions of CFQ-R forms in this study:

- CFQ-R for Children Ages 12 and 13 has a total of 35 questions to form 8 domains. All questions are scored 1, 2, 3, or 4.
- CFQ-R for Adolescents and Adults (subjects 14 years and older) has a total of 50 questions to form 12 domains. Question 43 is scored 1, 2, 3, 4, or 5 and is not used in calculating any domains; all the other 49 questions are scored 1, 2, 3, or 4.
- CFQ-R for Parents/Caregivers (subjects 13 years and younger) has a total of 44 questions to form 11 domains. Question 37 is scored 1, 2, 3, 4, or 5 and is not used in calculating any domains; all the other 43 questions are scored 1, 2, 3, or 4.

For all three CFQ-R versions, to calculate the score for each domain, the response scores on the negatively phrased questions are reversed (reversed scores = 5 – response scores) so that 1 always represents the worst condition and 4 always represents the best condition. In each domain, in cases where individual questions were skipped, the missing scores are imputed with the mean score of the non-missing questions for that domain rounded to the nearest integer.

The scaled score for each domain ranges from 0 (worst condition) to 100 (best condition) and is calculated as follows:

$$\text{Scaled score for a domain} = 100 \times (\text{mean}(\text{scores of all questions in that domain}) - 1)/3$$

The scaled score for a specific domain will not be calculated if more than half of the questions in the domain have missing scores.

Table 9-2, Table 9-3, and Table 9-4 provide the questions included in each domain, the questions with the reversed scores, as well as the maximum number of missing questions for the CFQ-R for Children Ages 12 and 13, the CFQ-R for Adolescents and Adults, and the CFQ-R for Parents/Caregivers respectively. [redacted]

**Table 9-2 CFQ-R for Children Ages 12 and 13**

| Domain | Questions | | Reversed questions | Maximum number of missing questions |
|---|---|---|---|---|
| | Total | Individual | | |
| Physical | 6 | 1, 2, 3, 4, 5, 6 | 1, 2, 3, 4, 5 | 3 |
| Emotion | 8 | 7, 8, 9, 10, 11, 12, 13, 14 | 14 | 4 |
| Social | 7 | 20, 21, 22, 23, 24, 25, 26 | 20, 22, 24, 26 | 3 |
| Body | 3 | 27, 28, 29 | - | 1 |
| Eat | 3 | 15, 17, 19 | 19 | 1 |
| Treatment burden | 3 | 16, 18, 30 | 18 | 1 |
| Respiration | 4 | 31, 32, 33, 34 | - | 2 |
| Digestion | 1 | 35 | - | 0 |

**Table 9-3 CFQ-R for Adolescents and Adults (subjects 14 years and older)**

| Domain | Questions | | Reversed questions | Maximum number of missing questions |
|---|---|---|---|---|
| | Total | Individual | | |
| Physical | 8 | 1, 2, 3, 4, 5, 13, 19, 20 | 13 | 4 |
| Role | 4 | 35, 36, 37, 38 | 35 | 2 |
| Vitality | 4 | 6, 9, 10, 11 | 6, 10 | 2 |
| Emotion | 5 | 7, 8, 12, 31, 33 | - | 2 |
| Social | 6 | 22, 23, 27, 28, 29, 30 | 23, 28, 30 | 3 |
| Body | 3 | 24, 25, 26 | - | 1 |
| Eat | 3 | 14, 21, 50 | - | 1 |

**Table 9-3 CFQ-R for Adolescents and Adults (subjects 14 years and older)**

| Domain | Questions | | Reversed questions | Maximum number of missing questions |
|---|---|---|---|---|
| | Total | Individual | | |
| Treatment burden | 3 | 15, 16, 17 | 15, 17 | 1 |
| Health perceptions | 3 | 18, 32, 34 | 18, 32, 34 | 1 |
| Weight | 1 | 39 | - | 0 |
| Respiration* | 6 | 40, 41, 42, 44, 45, 46 | 43 | 3 |
| Digestion | 3 | 47, 48, 49 | - | 1 |

*: Question 43 not used to calculate a domain.

**Table 9-4 CFQ-R for Parents/Caregivers (subjects 13 years and younger)**

| Domain | Questions | | Reversed questions | Maximum number of missing questions |
|---|---|---|---|---|
| | Total | Individual | | |
| Physical | 9 | 1, 2, 3, 4, 5, 13, 14, 15, 16 | 15 | 4 |
| Vitality | 5 | 8, 9, 10, 11, 12 | 10, 12 | 2 |
| Emotion | 5 | 6, 7, 23, 25, 26 | 6 | 2 |
| School | 3 | 27, 28, 29 | 28 | 1 |
| Body | 3 | 19, 20, 21 | - | 1 |
| Eat | 2 | 17, 44 | - | 0 |
| Treatment burden | 3 | 18, 30, 31 | 31 | 1 |
| Health perceptions | 3 | 22, 24, 32 | 22, 24, 32 | 1 |
| Weight | 1 | 33 | - | 0 |
| Respiration* | 6 | 34, 35, 36, 38, 39, 40 | 37 | 3 |
| Digestion | 3 | 41, 42, 43 | - | 1 |

*: Question 37 not used to calculate a domain.

The absolute change from baseline in the respiratory domain of the CFQ-R (Pooled 'Children Ages 12 and 13' Version and 'Adolescents and Adults' Version) at Week 24 is one of the secondary endpoints.

**Absolute change from baseline in overall Patient Health Questionnaire (PHQ-8) and Generalized Anxiety Disorder (GAD-7) scores at Week 24**

Defined as overall Patient Health Questionnaire (PHQ-8) and Generalized Anxiety Disorder (GAD-7) scores at Week 24 minus overall Patient Health Questionnaire (PHQ-8) and Generalized Anxiety Disorder (GAD-7) scores at baseline, correspondingly

Both GAD-7 and PHQ-8 will be summarized by proportion of patients in each severity category at both baseline and Week 24. The detailed information with regard to these two scores and the severity category is indicated below.

**PHQ-8 Depression Severity.** This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of ―not at all, ―several days, ―more than half the days, and ―nearly every day, respectively. PHQ-8 total score for the eight items ranges from 0 to 24. Scores of 5, 10, 15, and 20 represent cutpoint for mild, moderate, moderately severe and severe depression, respectively. Sensitivity to change has also been confirmed.

**GAD-7 Anxiety Severity.** This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of ―not at all, ―several days, ―more than half the days, and ―nearly every day, respectively. GAD-7 total score for the seven items ranges from 0 to 21. Scores of 5, 10, and 15 represent cutpoint for mild, moderate, and severe anxiety, respectively. Though designed primarily as a screening and severity measure for generalized anxiety disorder, the GAD-7 also has moderately good operating characteristics for three other common anxiety disorders – panic disorder, social anxiety disorder, and post-traumatic stress disorder. When screening for anxiety disorders, a recommended cutpoint for further evaluation is a score of 10 or greater.

[redacted]

**Absolute change from baseline in physical activity as determined by actigraphy at Week 24**

Defined as total activity count at Week 24 minus total activity count at baseline. Baseline is defined as the daily mean of data obtained in the 7 days prior to Day 1 (Day -7 through Day -1). Week 24 is defined as the mean of data obtained in the calendar week prior to Week 24.

**Relative change from baseline in physical activity as determined by actigraphy at Week 24**

Defined as total activity count at Week 24 minus total activity count at baseline, divided by total activity count at baseline. Baseline is defined as the daily mean of data obtained in the 7 days prior to Day 1 (Day -7 through Day -1). Week 24 is defined as the mean of data obtained in the calendar week prior to Week 24 visit.

**Absolute change from baseline in duration of sleep time during the night at Week 24**

Defined as average duration of sleep time at Week 24 minus average duration of sleep time at baseline. Baseline is defined as the daily mean of data obtained in the 7 days prior to Day 1 (Day -7 through Day -1).; week 24 is defined as the mean of data obtained in the calendar week prior to Week 24 visit.

**Relative change from baseline in duration of sleep time during the night at Week 24**

Defined as average duration of sleep time at Week 24 minus average duration of sleep time at baseline, divided by average duration of sleep time at baseline. Baseline is defined as the

daily mean of data obtained in the 7 days prior to Day 1 (Day -7 through Day -1).; week 24 is defined as the mean of data obtained in the calendar week prior to Week 24 visit.

**Absolute change from baseline in time above sedentary duration at Week 24**

Defined as average time above sedentary duration at Week 24 minus average time above sedentary duration at baseline. Baseline is defined as the daily mean of data obtained in the 7 days prior to Day 1 (Day -7 through Day -1).; week 24 is defined as the mean of data obtained in the calendar week prior to Week 24 visit.

**Relative change from baseline in time above sedentary duration at Week 24**

Defined as average time above sedentary duration at Week 24 minus average time above sedentary duration at baseline, divided by average time above sedentary duration at baseline. Baseline is defined as the daily mean of data obtained in the 7 days prior to Day 1 (Day -7 through Day -1).; week 24 is defined as the mean of data obtained in the calendar week prior to Week 24 visit.

The time unit for duration of sleep and time above sedentary duration will be in hours.

[redacted]

#### 9.3.2.2 Analysis of Secondary Endpoints

##### 9.3.2.2.1 Analysis of Key Secondary Efficacy Endpoints

**Absolute and percentage change from baseline in exercise duration during CPET at Week 24**

Analysis of these two variables will be similar to that of the primary analysis of the primary efficacy endpoint using a mixed model repeated measures (MMRM) using SAS PROC MIXED based on the FAS, with the exception that exercise duration during CPET at baseline will replace baseline $VO_2$max value in the MMRM model.

Absolute and percentage change from baseline in exercise duration measured in the unit of seconds at both Week 12 and Week 24 will be derived from the main model based on the FAS. The LS means (with 95% CI) at each visit will be plotted by treatment groups.

In addition, raw changes from baseline in exercise duration measured in the unit of seconds as well as raw values at both Week 12 and Week 24 will be summarized using descriptive summary statistics.

##### 9.3.2.2.2 Analysis of Additional Secondary Efficacy Endpoints

Analysis of the following other secondary endpoints will also be similar to that of the primary analysis of the primary efficacy endpoint using a mixed model repeated measures (MMRM) using SAS PROC MIXED based on the FAS, with the exception that for each of these secondary endpoints, their corresponding value at baseline will replace baseline $VO_2$max value in the MMRM model.

- Absolute change from baseline in $VO_2$max during cardiopulmonary exercise testing (CPET) at Week 24
- Absolute and relative change from baseline in oxygen consumption ($VO_2$) at anaerobic threshold (AT) (the point during exercise at which lactate starts to accumulate) at Week 24
- Absolute and relative change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at Week 24. Note: Baseline $ppFEV_1$ will not be included in the MMRM model because $ppFEV_1$ at baseline as a stratification factor has already been included in the model.
- Absolute and relative change from baseline in body mass index (BMI) at Week 24

- Absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score at Week 24
- Absolute and relative change from baseline in functional $VO_2$ gain at Week 24
- Absolute and relative change from baseline in the slope of pulmonary ventilation (VE) versus carbon dioxide production ($VCO_2$) at Week 24

Absolute and percentage change from baseline in these other secondary endpoints above at both Week 12 and Week 24 will be derived from the main model based on the FAS.

In addition, raw changes from baseline in these other secondary endpoints above as well as raw values at both Week 12 and Week 24 will be summarized using descriptive summary statistics.

Analysis of the following other secondary endpoints will be based on descriptive summary statistics only. Descriptive summary statistics along with 95% confidence interval will be provided at both Week 12 and Week 24 by treatment groups.

- Absolute change from baseline in overall Patient Health Questionnaire (PHQ-8) and Generalized Anxiety Disorder (GAD-7) scores at Week 24
- Proportion of patients in each severity category of PHQ-8 and GAD-7 scores at both baseline and Week 24.
- Absolute and relative change from baseline in physical activity as determined by actigraphy at Week 24
- Absolute and relative change from baseline in duration of sleep time during the night at Week 24
- Absolute and relative change from baseline in time above sedentary duration at Week 24

In addition, raw values from baseline in these other secondary endpoints above as well as raw values at both Week 12 and Week 24 will be summarized using descriptive summary statistics.

[redacted]

#### 9.3.2.3 Correlation analysis

Correlation analysis using both Pearson's correlation coefficient and Spearman's correlation coefficient will be evaluated for the following endpoints for their corresponding change from baseline to week 24. Correlation analysis will be performed by treatment arms as well as in the overall patient population.

Percentage change of VO2max and percentage change of ppFEV1

Absolute change of VO2max and absolute change of ppFEV1

Percentage change of exercise duration and percentage change of ppFEV1

Absolute change of exercise duration and absolute change of ppFEV1

Absolute change of $VO_2$ at AT and absolute change of ppFEV1

Percentage change of $VO_2$ at AT and percentage change of ppFEV1

Absolute change of functional $VO_2$ gain and absolute change of ppFEV1

Percentage change of functional $VO_2$ gain and percentage change of ppFEV1

Absolute change of the slope of pulmonary ventilation (VE) versus carbon dioxide production ($VCO_2$) and absolute change of ppFEV1

Percentage change of the slope of pulmonary ventilation (VE) versus carbon dioxide production ($VCO_2$)and percentage change of ppFEV1

Absolute change of sleeping time and absolute change of ppFEV1

Absolute change of physical activity and absolute change of ppFEV1

Absolute change of time above sedentary duration and absolute change of ppFEV1

#### 9.3.2.4 Multiplicity adjustment

No multiplicity adjustment will be made in this study.

### 9.4 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, urinalysis, and coagulation studies)

Safety endpoints will be analyzed based on the Safety Set. Only descriptive analysis of safety will be performed (i.e., no statistical testing will be performed).

The study period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period after the informed consent/assent date and before the initial dosing of study drug.
- The **treatment-emergent period** is the period at or after the initial dosing (including day 1) of study drug to 28 days after the last dose of study drug.
- The **post-treatment period** is defined as the period after 28 days after last dose until the end of study.

### 9.4.1 Adverse Events

For analysis purpose, AEs will be categorized as pretreatment AEs, treatment-emergent adverse events (TEAEs), or post-treatment AEs:

- **Pretreatment AE:** any AE that started before initial dosing of study drug.
- **TEAE:** any AE that increased in severity or that was newly developed at or after the initial dosing of study drug to the end of the safety follow up period.
- **Post-treatment AE:** any AE that increased in severity or that was newly developed after 28 days after the last dose of study drug.

For AEs with missing or partial start dates, if there is no clear evidence that the AEs started before or after study treatment, then the AEs will be classified as TEAEs.

As an intermediate step for programming purposes, imputation rules for missing or partially missing AE start/end dates are defined below:

- If year of the AE start date is missing, then query site with no imputation.
- If year of the AE start date is not missing, but both day and month of the AE start date are missing
    - If year of the AE start date = the year of the first dose date, impute the missing day and month of the AE start date using the day and month of the first dose date. If this leads to a date after the AE end date, then impute the missing day and month of the AE start date using the day and month of the AE end date. Note:
        - If the AE ended before first dose date, then the AE will be classified as a pre-treatment AE. If the AE ended after the first dose date, then there is not enough evidence to determine whether the AE is a TEAE or not, and to be conservative, the AE will be classified as a TEAE.
    - If year of the AE start date ≠ the year of the first dose date, impute the missing day and month of the AE start date using 1 and Jan. Note:
        - If the year is before the year of the first dose date, then by imputing the missing day and month of the AE start date January 1, TEAE status will be pre-treatment.
        - If the year is after the year of the first dose date, then by imputing the missing day and month of the AE start date January 1, TEAE status will be TEAE if AE

start date is on or before the last dose date +28 days; and will be post-treatment AE start date is after the last dose date+28 days.

- If month and year of the AE start date are not missing, but day of the AE start date is missing
  - If the year of the AE start date = the year of the first dose date = the year of the AE end date, and the month of the AE start date = the month of the first dose date = the month of the AE end date, then impute the missing day of AE start date using the smaller non-missing value of (day of the first dose, day of the AE end date).
  - If (the year of the AE start date = the year of the first dose date, and the month of the AE start date = the month of the first dose date), and (the year of the AE start date < the year of the AE end date, or the month of the AE start date < the month of the AE end date), then impute the missing day of AE start date using the day of the first dose.
  - Otherwise, impute the missing day of the AE start date as 1.
- Missing or partially missing AE stop date will not be imputed.

An overview of the TEAE profile will be provided with number and percent of subjects including the following categories:

- Number of TEAEs (total number of TEAEs only)
- All TEAEs
- TEAEs by relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Serious TEAEs
- Related serious TEAEs
- TEAE leading to death

Adverse events summary tables will be presented for TEAEs only and will include the following:

- All TEAEs
- TEAEs by relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Serious TEAEs
- Related serious TEAEs

- TEAEs 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 worst/highest relationship level in the relationship summaries.

Additional summary tables will be presented for TEAEs showing number and percentage of subjects

- Any TEAE by PT
- Respiratory TEAE
- TEAE with a frequency of ≥5% at the PT level in any treatment group by PT
- TEAE with a frequency of ≥5% at the PT level in any treatment group by SOC and PT

In addition, a listing containing individual subject adverse event data for TEAEs leading to treatment discontinuation and treatment interruption, SAEs and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.

### 9.4.2 Clinical Laboratory

For the laboratory measurements, the raw values and change from baseline values of the continuous hematology and chemistry results will be summarized in SI units by treatment group at each scheduled time point. For hematology and chemistry, the number and percentage of subjects with abnormal low (<LLN) value and with abnormal high (>ULN) value at each scheduled time point will be summarized.

The number and percentage of subjects with at least one potentially clinically significant (PCS) event for liver enzyme during the treatment-emergent period will be summarized. The PCS criteria are provided in Appendix F.

For all LFT results (alanine aminotransferase [ALT], aspartate aminotransferase [AST], serum alkaline phosphatase [ALP], Gamma-glutamyl transferase[GGT] and total bilirubin), the following analyses will be conducted:

- For each of the LFTs, mean values (and 95% confidence interval) will be plotted against visit, and box plot of LFT value/ULN will be plotted against visit.
- The incidence of PCS LFTs during the treatment-emergent period according to the baseline status will also be summarized by treatment group (only worsening of the shift from baseline will be presented).
- A listing of subjects with elevated LFT results during the treatment-emergent period will be presented. The listing will include all parameters of the LFT assessment at all visits.

Results of urinalysis and the serum pregnancy test will be listed in individual subject data listings only. In addition, a listing containing individual subject hematology, chemistry, and

coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

### 9.4.3 Vital Signs

For the vital signs measurements, the raw values and change from baseline values will be summarized by treatment group at each scheduled time point: systolic and diastolic blood pressure (mm Hg)

The number and percentage of subjects with at least one PCS vital signs event during the treatment-emergent period will be summarized. The PCS criteria are provided in Appendix F

### 9.4.4 Pulse Oximetry

For the on-treatment pulse oximetry measurements taken at each CPET before the start of any exercise , a summary of raw values and change from baseline values will be provided by treatment groups at each scheduled time point for the percent of oxygen saturation by pulse oximetry. In addition, the mean value at each visit will be plotted by treatment groups for the percent of oxygen saturation.

### 9.4.5 Physical Examination

PE findings, which are only collected at Screening in the database, will be presented as a data listing only.

### 9.4.6 Ophthalmologic Examination

Abnormal ophthalmologic examination findings will be presented as a data listing only.

## 9.5 Narratives Listings

Narratives listings will be provided for subjects with any of the following events that occurred by the study cutoff date:

- Death
- Serious TEAEs
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Pregnancy

# 10 INTERIM AND DMC ANALYSES

## 10.1 Interim Analysis

No interim analysis is planned.

## 10.2 DMC Analysis

No DMC analysis is planned

# 11 REFERENCES

1 Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol. 1993; 15:75-88.

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

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

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

# 12 APPENDICES

## Appendix A Schedule of Assessments

**Table 12-1Study VX15-809-112: Treatment Period and Safety Follow-up Visit**

| Event/Assessment | Treatment Period | | | Early Termination of Treatment[a] | Safety Follow-up 4 Weeks (± 7 Days) After Last Dose[a] |
|---|---|---|---|---|---|
| | Day 1 | Week 12 (± 7 Days) | Week 24 (± 7 Days) | | |
| Clinic Visit | X | X | X | X | X |
| Randomization | X | | | | |
| CFQ-R, PHQ-8, and GAD-7[b] | X | X | X | X | |
| Height and weight[c] | X | X | X | X | X |
| Vital signs[d] | X | X | X | X | X |
| Spirometry[e] | X | X | X | X | |
| Physical examination (PE)[f] | X | | | | X |
| Ophthalmologic examination | | | X[g] | X[g] | X[g] |
| Cardiopulmonary exercise test (CPET)[h] | X | X | X | X | |
| Urine β-HCG[i] | X | X | X | X | X |
| Serum chemistry[j] | X | X | X | X | X |
| Hematology[j] | X | X | X | X | X |

[a] If the subject prematurely discontinues study drug, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the subject decides to discontinue. If the ETT Visit occurs 3 weeks after the last dose of study drug or later, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required. When the Safety Follow-up Visit is complete, the subject has completed the study.

[b] All questionnaires must be completed before the start of any other assessments scheduled at that visit. The CFQ-R must be completed first, then the PHQ-8 and GAD-7.

[c] During the Treatment Period and at the Safety Follow-up Visit, height will be collected only for subjects who were 21 years of age or younger at the Screening Visit. Height and weight will be measured with shoes off.

[d] Vital signs (systolic and diastolic blood pressure, oral temperature, pulse rate, and respiration rate) will be collected before study drug dosing and after the subject has been seated for at least 5 minutes. Blood pressure will be taken using a manual sphygmomanometer.

[e] Spirometry will be assessed before CPET.

[f] The physical examination includes an assessment of all body systems. Symptom-directed physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

[g] For all subjects <18 years of age at the Screening Visit, except for those who have had bilateral lens removal, an ophthalmologic examination will be conducted by a licensed ophthalmologist or optometrist at 1 of the following visits: the Week 24 Visit, the ETT Visit, or the Safety Follow-up Visit.

[h] CPET includes pulse oximetry.

[i] Pregnancy tests will be performed for all female subjects of childbearing potential. A urine β–hCG test will be performed on Day 1 (before first dose of study drug) and every 4 weeks thereafter. When there is not a scheduled study visit, the pregnancy test will be conducted with a urine home pregnancy test kit provided by the study site. For tests performed at home, the site staff will telephone the subject to confirm the test results.

[j] On Day 1, blood samples for chemistry and hematology tests will be collected before the first dose of study drug. At other scheduled visits, these samples may be collected at any time during the visit.

## Table 12-1Study VX15-809-112: Treatment Period and Safety Follow-up Visit

| Event/Assessment | Treatment Period | | | Early Termination of Treatment[a] | Safety Follow-up 4 Weeks (± 7 Days) After Last Dose[a] |
|---|---|---|---|---|---|
| | Day 1 | Week 12 (± 7 Days) | Week 24 (± 7 Days) | | |
| Study drug dispensed[k] | X | X | | | |
| Study drug dosing | LUM 400 mg/IVA 250 mg q12h **or** placebo q12h | | | | |
| Study drug count | | X | X | X | |
| Reminder of standard exercise recommendations[l] | X | X | | | |
| Activity and sleep tracking via actigraphy | Continuous from Day 1 through Week 24 Visit | | | | |
| Recording concomitant medications and treatments/procedures | Continuous from signing of ICF through Safety Follow-up Visit | | | | |
| Recording AEs | Continuous from signing of ICF through Safety Follow-up Visit | | | | |

[redacted]

[k] Study drug will be administered orally, 2 times a day, within 30 minutes of consumption of fat-containing food..
[l] [redacted]

## Appendix B Precisions of Summary for Continuous Variables

**Continuous Variables**

**Table 12-2 Precision of Special Summary Statistics for CF Studies**

| Variables | Statistics | Decimal Places |
|---|---|---|
| CPET Related variables | Mean, LS mean, 95% CI | 1 |
| Percent Predicted $FEV_1$ | Mean, LS mean, 95% CI | 1 |
| CFQ-R | Mean, LS mean, 95% CI | 1 |
| BMI | Mean, LS mean, 95% CI | 1 |
| PHQ-8/GAD-7 | Mean, 95% CI | 1 |
| Demographics | Mean, 95% CI | 1 |
| [redacted] | | |
| Actigraphy | Mean, 95% CI | 1 |

The precision of the Safety Lab Data will follow the latest standard from the Biometrics Standardization Committee.

The precision of the measurement in raw data for other continuous variables will be used to determine the number of decimal places to present in tables, figures, and derived listings. Minimum and maximum values will be reported with the same precision as the units of measure. The mean and median will be reported to 1 greater decimal place, and the SD and SE will be reported to 2 additional decimal places.

Any values that require transformation to standard units (metric or International System [SI]) will be converted with the appropriate corresponding precision.

# Appendix C Analysis Visit Window Mapping Rules for Safety and Pharmacodynamic and Actigraphy Measurements

**Table 12-3 Visit Window Mapping Rules for Safety and Pharmacodynamic and Actigraphy Measurements**

| Assessments | Visit | Target Study Day | Visit Window (in study days) |
|---|---|---|---|
| • CPET related | Week 12 | 85 | (1, 92] |
| • | Week 24 | 169 | [93, 176] |
| • Spirometry | Safety follow up week 28 | 197 | [177, 204] |
| • | | | |
| • CFQ-R/PHQ-8/GAD-7 | | | |
| • | | | |
| • Weight and Height | | | |
| • | | | |
| • Vital Signs | | | |
| • | | | |
| • Actigraphy* | | | |
| • | | | |
| • Labs – Liver Function Test | | | |

* Baseline actigraphy data will be the average of the corresponding actigraphy data 7 days prior to the Day 1 visit (Day -7 to Day -1). The same rule applies to actigraphy data collected at week 12 and week 24, where the average of the corresponding actigraphy data 7 days prior to the target day visit (target study Days 85 and 169 will be used for these two visits). Due to a window of ± 7 Days for each of these visits, the actual 7-day interval from which actigraphy data is used may vary from subject to subject.

# Appendix D Coefficients for Hankinson and Wang Methods 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] and Wang[2] standards.

The Hankinson standard will be applied to male subjects 18 years and older and female subjects 16 years and older; the Wang standard will be applied to male subjects 6 to 17 years and female subjects 6 to 15 years of age. During the study, the subjects who have a birthday that would move them from Wang to Hankinson will use the Wang standard before that birthday and the Hankinson standard at or after that birthday.

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 12-4

Wang Normal Values (WNVs) will be calculated for $FEV_1$, FVC, $FEF_{25-75\%}$, and $FEV_1$/FVC using the Wang equation:

$$\ln(\text{Predicted lung function parameter}) = \alpha + \beta \ln(\text{height})$$

Wang Normal Values (WNVs) will be calculated for $FEV_1$, FVC, $FEF_{25-75\%}$, and $FEV_1$/FVC using the Wang equation. In the equation, height is given in meters, and the coefficients $\alpha$ and $\beta$ are determined based on subject's sex, race, and age as shown in Table 12-5 and Table 12-6.

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 12-4 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 1

**Table 12-5 WNVs Equation Coefficients by Sex and Age in White Boys and Girls**

| | | $FEV_1$ | | FVC | | $FEF_{25-75\%}$ | | $FEV_1/FVC$ | |
|---|---|---|---|---|---|---|---|---|---|
| **Sex** | **Age** | **α** | **β** | **α** | **β** | **α** | **β** | **α** | **β** |
| Male | 6 | -0.109 | 2.252 | -0.024 | 2.470 | | | -0.078 | -0.248 |
| | 7 | -0.104 | 2.270 | -0.018 | 2.489 | | | -0.086 | -0.220 |
| | 8 | -0.089 | 2.257 | 0.005 | 2.443 | 0.264 | 1.505 | -0.091 | -0.199 |
| | 9 | -0.063 | 2.197 | 0.017 | 2.426 | 0.308 | 1.443 | -0.086 | -0.206 |
| | 10 | -0.057 | 2.212 | 0.030 | 2.407 | 0.290 | 1.557 | -0.081 | -0.209 |
| | 11 | -0.093 | 2.324 | 0.009 | 2.468 | 0.242 | 1.738 | -0.101 | -0.147 |
| | 12 | -0.161 | 2.512 | -0.061 | 2.649 | 0.165 | 1.982 | -0.101 | -0.133 |
| | 13 | -0.292 | 2.843 | -0.175 | 2.924 | 0.007 | 2.396 | -0.116 | -0.085 |
| | 14 | -0.329 | 2.983 | -0.219 | 3.060 | 0.014 | 2.483 | -0.106 | -0.087 |
| | 15 | -0.141 | 2.709 | -0.079 | 2.859 | 0.241 | 2.163 | -0.060 | -0.155 |
| | 16 | 0.062 | 2.409 | 0.104 | 2.591 | 0.503 | 1.764 | -0.045 | -0.178 |
| | 17 | 0.262 | 2.099 | 0.253 | 2.374 | 0.762 | 1.368 | 0.008 | -0.272 |
| Female | 6 | -0.109 | 1.949 | -0.013 | 2.007 | | | -0.097 | -0.055 |
| | 7 | -0.144 | 2.243 | -0.062 | 2.385 | | | -0.084 | -0.132 |
| | 8 | -0.137 | 2.239 | -0.055 | 2.381 | 0.247 | 1.668 | -0.079 | -0.152 |
| | 9 | -0.123 | 2.222 | -0.039 | 2.351 | 0.254 | 1.710 | -0.084 | -0.128 |
| | 10 | -0.161 | 2.364 | -0.068 | 2.458 | 0.195 | 1.933 | -0.092 | -0.097 |
| | 11 | -0.223 | 2.558 | -0.120 | 2.617 | 0.161 | 2.091 | -0.102 | -0.061 |
| | 12 | -0.264 | 2.709 | -0.174 | 2.776 | 0.185 | 2.120 | -0.090 | -0.067 |
| | 13 | -0.153 | 2.535 | -0.061 | 2.576 | 0.294 | 1.976 | -0.093 | -0.040 |
| | 14 | 0.046 | 2.178 | 0.139 | 2.208 | 0.450 | 1.711 | -0.096 | -0.026 |
| | 15 | 0.148 | 2.008 | 0.210 | 2.099 | 0.581 | 1.486 | -0.062 | -0.093 |

Source: Reference 1

**Table 12-6 WNVs Equation Coefficients by Sex and Age in Black Boys and Girls**

| | | $FEV_1$ | | FVC | | $FEF_{25-75\%}$ | | $FEV_1/FVC$ | |
|---|---|---|---|---|---|---|---|---|---|
| **Sex** | **Age** | **α** | **β** | **α** | **β** | **α** | **β** | **α** | **β** |
| Male | 6 | -0.166 | 1.723 | -0.088 | 1.961 | | | -0.091 | -0.152 |
| | 7 | -0.122 | 1.846 | -0.040 | 2.040 | | | -0.091 | -0.153 |
| | 8 | -0.225 | 2.271 | -0.094 | 2.323 | 0.097 | 1.544 | -0.118 | -0.104 |
| | 9 | -0.142 | 2.059 | -0.074 | 2.308 | 0.255 | 1.248 | -0.079 | -0.218 |
| | 10 | -0.157 | 2.117 | -0.110 | 2.417 | 0.230 | 1.428 | -0.047 | -0.303 |
| | 11 | -0.176 | 2.166 | -0.138 | 2.453 | 0.256 | 1.438 | -0.048 | -0.263 |
| | 12 | -0.307 | 2.548 | -0.224 | 2.710 | 0.085 | 1.936 | -0.084 | -0.162 |
| | 13 | -0.486 | 2.962 | -0.342 | 2.975 | -0.121 | 2.476 | -0.141 | -0.018 |
| | 14 | -0.472 | 3.010 | -0.337 | 3.035 | -0.115 | 2.536 | -0.123 | -0.050 |
| | 15 | -0.318 | 2.789 | -0.226 | 2.889 | 0.170 | 2.120 | -0.070 | -0.140 |
| | 16 | 0.074 | 2.140 | 0.058 | 2.425 | 0.663 | 1.299 | 0.018 | -0.289 |
| | 17 | 0.053 | 2.223 | 0.148 | 2.310 | 0.505 | 1.618 | -0.095 | -0.087 |
| Female | 6 | -0.288 | 2.182 | -0.172 | 2.117 | | | -0.109 | 0.059 |
| | 7 | -0.250 | 2.158 | -0.135 | 2.132 | | | -0.104 | -0.030 |
| | 8 | -0.276 | 2.295 | -0.176 | 2.362 | -0.283 | 2.990 | -0.103 | -0.066 |
| | 9 | -0.294 | 2.330 | -0.200 | 2.452 | 0.025 | 2.062 | -0.097 | -0.104 |
| | 10 | -0.344 | 2.507 | -0.230 | 2.571 | 0.051 | 2.028 | -0.120 | -0.043 |
| | 11 | -0.308 | 2.460 | -0.204 | 2.526 | 0.078 | 2.006 | -0.089 | -0.105 |
| | 12 | -0.219 | 2.312 | -0.107 | 2.342 | 0.225 | 1.804 | -0.115 | -0.021 |
| | 13 | -0.117 | 2.196 | -0.042 | 2.294 | 0.418 | 1.504 | -0.051 | -0.148 |
| | 14 | 0.041 | 1.920 | 0.105 | 2.021 | 0.574 | 1.257 | -0.063 | -0.103 |
| | 15 | 0.203 | 1.662 | 0.253 | 1.787 | 0.599 | 1.281 | -0.043 | -0.139 |

Source: Reference 2 (Tables 4 and 5)

# Appendix F Criteria for Potentially Clinically Significant Events

## Table 12-7 Criteria for Potentially Clinically Significant Laboratory Tests

| Parameter | PCS | Comments |
|---|---|---|
| **Clinical Chemistry** | | |
| ALT | ≤3xULN*(Not a PCS criteria)<br>>3x - ≤ 5xULN<br>>5x - ≤ 8xULN<br>>3xULN<br>>5xULN<br>>8xULN | FDA DILI Guidance Jul 2009. |
| AST | ≤3xULN*(Not a PCS criteria)<br>>3x - ≤ 5xULN<br>>5x - ≤ 8xULN<br>>3xULN<br>>5xULN<br>>8xULN | FDA DILI Guidance Jul 2009. |
| ALT or AST | ALT>3xULN or AST>3xULN | Vertex LFT working group 2014 |
| Alkaline Phosphatase | >1.5xULN | FDA DILI Guidance Jul 2009. |
| Total Bilirubin | >1.5x - ≤2xULN<br>>2xULN | FDA DILI Guidance Jul 2009. |
| ALT and Total Bilirubin | ALT>3xULN and TBILI>2xULN | FDA DILI Guidance Jul 2009.<br>To be counted within a same treatment phase, whatever the interval between measurement. |
| AST and Total Bilirubin | AST>3xULN and TBILI>2xULN | FDA DILI Guidance Jul 2009.<br>To be counted within a same treatment phase, whatever the interval between measurement. |
| (ALT or AST) and Total Bilirubin | (ALT>3xULN or AST>3xULN) and TBILI>2×ULN | Vertex LFT working group 2014 |

**Table 12-8 Criteria for Potentially Clinically Significant Vital Signs**

| CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT VITAL SIGNS | | |
|---|---|---|
| **Parameter** | **PCS** | **Comments** |
| HR | ≤50 bpm and decrease from baseline ≥20 bpm<br>≥120 bpm and increase from baseline≥20 bpm | To be applied for all positions (including missing) except STANDING. |
| SBP | >140 mmHg at least once<br>>160 mmHg at least once<br>>140 mmHg at least twice<br>>10 mmHg increase from Baseline at least once<br>>20 mmHg increase from Baseline at least once | To be applied for all positions (including missing) except STANDING. |
| DBP | >90 mmHg at least once<br>>100 mmHg at least once<br>>90 mmHg at least twice<br>>5 mmHg increase from Baseline at least once<br>>10 mmHg increase from Baseline at least once | To be applied for all positions (including missing) except STANDING. |

# Appendix G Important Protocol Deviation Programming Rules (Based on the Clinical Database)

## Important protocol deviations before first dose

1. Individual screening assessment(s) that did not meet eligibility criteria, excluding the exceptions that are permitted per protocol, were repeated
2. Screening visit performed outside of the -28 to -1 day window
3. Subject randomized and screening ophthalmologic examination greater than 3 months prior to Screening Visit
4. Height not collected for subjects who were 21 years of age or younger at the Screening Visit.

## Important protocol deviations during treatment period

5. ETT visit was less than 3 weeks after the last dose of study drug but no Safety Follow-up Visit was performed.
6. After subject study completion/early discontinuation, prior study visits not done
7. Subject who prematurely discontinues study drug treatment did not complete the ETT visit
8. CPET not performed per protocol schedule
9. Prohibited medication taken during study
10. Initial dose of study drug not administered on Day 1.