1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

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

Vertex Study Number: VX15-809-112

[redacted]

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Vertex Pharmaceuticals Incorporated
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2 PROTOCOL SYNOPSIS

Title

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

Brief Title

A Study of the Effects of Lumacaftor/Ivacaftor on Exercise Tolerance in Subjects With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

Clinical Phase and Clinical Study Type

Phase 4, investigation of exercise tolerance

Objectives

Primary Objective

To evaluate the effect of lumacaftor/ivacaftor (LUM/IVA) combination therapy on exercise tolerance in subjects with cystic fibrosis (CF), homozygous for the *F508del-CFTR* mutation

Secondary Objective

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

Endpoints

Primary Endpoint

Percentage change from baseline in maximal oxygen consumption (VO_{2max}) during cardiopulmonary exercise testing (CPET) at Week 24

Secondary Endpoints

Key Secondary Endpoint

Change from baseline in exercise duration during CPET at Week 24

Other Secondary Endpoints

- Change from baseline in oxygen consumption (VO_2) at anaerobic threshold (AT) (the exercise intensity at which lactate starts to accumulate) at Week 24
- Change from baseline in functional VO_2 gain at Week 24
- Change from baseline in the pulmonary ventilation (VE) versus carbon dioxide production (VCO_2) slope at Week 24
- Change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at Week 24
- Change from baseline in body mass index (BMI) at Week 24
- Change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score at Week 24
- Change from baseline in overall Patient Health Questionnaire (PHQ-8) and Generalized Anxiety Disorder (GAD-7) scores at Week 24
- Change from baseline in physical activity as determined by actigraphy at Week 24
- Change from baseline in duration of sleep time and change in sleep quality during the night at Week 24
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values (serum chemistry and hematology), vital signs, and ophthalmologic examinations (for subjects under 18 years of age only).

[redacted]

Number of Subjects Approximately 66

Study Population Male and female subjects, aged 12 years and older, with a confirmed diagnosis of CF, homozygous for the *F508del-CFTR* mutation.

Investigational Drug Active substance: LUM/IVA (fixed-dose combination tablet containing LUM and IVA)

Activity: CFTR corrector and potentiator (chloride ion [Cl^-] secretion)

Strength and route of administration: LUM 200 mg/IVA 125 mg fixed-dose combination tablets for oral administration

Dosage: LUM 400 mg every 12 hours (q12h)/IVA 250 mg q12h

Study Duration Excluding the Screening Period, each subject will participate in the study for 28 (± 1) weeks, including 24 weeks on study drug and a 4-week follow-up.

Study Design Phase 4, randomized, double-blind, placebo-controlled, parallel-group study. Subjects will receive study drug (LUM/IVA or placebo) in addition to their current CF medication regimen. It is recommended that subjects remain on a stable medication regimen for their CF from 4 weeks before Day 1 through the Safety Follow-up Visit.

[redacted]

Assessments

Efficacy Assessments

- VO_2, AT, and VE as determined by the CPET
- Spirometry parameters, including FEV_1, forced vital capacity (FVC), FEV_1/FVC ratio, and forced expiratory flow ($FEF_{25\%-75\%}$)
- Actigraphy to monitor activity level and sleep duration and quality
- BMI to monitor nutritional status
- Questionnaires pertaining to quality of life, depression, and anxiety: CFQ-R, PHQ-8, and GAD-7

Safety Assessments

AEs, clinical laboratory assessments, clinical evaluation of vital signs, ophthalmologic examinations (for subjects under 18 years of age only), and physical examinations. Spirometry data will also be used as safety-supporting data.

[redacted]

Statistical Analyses

Statistical analysis details will be provided in the statistical analysis plan (SAP). The Vertex Biometrics department or a designated contract research organization will analyze the data derived from this study.

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. Sample sizes needed for 80% power under various conditions are shown in Section 12.1.

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

Analysis Sets

The Full Analysis Set (FAS) is defined as all randomized subjects who have received at least 1 dose of study drug. The FAS will be used for all efficacy analyses, with subjects analyzed according to their randomized treatment group.

The Safety Set is defined as 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.

Efficacy Analyses

For the primary analysis, the null hypothesis is that the mean percentage change from study baseline in VO_{2max} at Week 24 is the same for the LUM/IVA and placebo groups.

The primary analysis will use a restricted maximum likelihood (REML)-based mixed effect model for repeated measures (MMRM). The model will include the percentage change from baseline in VO_{2max} as the dependent variable; treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect with adjustment for sex (male versus female), age group at baseline (<18 versus ≥18 years old), and $ppFEV_1$ at Screening (<70% versus ≥70%).

The primary result obtained from the model will be the estimated treatment effect at Week 24 based on a contrast test. The estimated mean treatment effect at Week 24, a 95% confidence interval, and a 2-sided *P* value will be provided.

Secondary endpoints will be analyzed in a similar fashion.

Safety Analyses

The overall safety profile of study treatments will be assessed in terms of the following safety endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values
- Vital signs
- Ophthalmologic examinations (for subjects under 18 years of age only)

For safety variables, the scheduled Day 1, predose measurement will be used as the baseline value, when available; otherwise, the baseline value will be defined as the value at the Screening Visit.

All safety data will be listed by subject in data listings.

Summaries of TEAEs will be presented by MedDRA system organ class and preferred term using frequency counts and percentages. Summaries will be presented for all TEAEs, TEAEs by relationship, TEAEs by maximum severity, TEAEs leading to treatment discontinuation, serious TEAEs, TEAEs leading to death, and frequently reported TEAEs.

3 SCHEDULE OF ASSESSMENTS

Schedules of Assessments are shown in Table 3-1 and Table 3-2.

Table 3-1 Study VX15-809-112: Screening

Assessment	Screening Visit Day -28 to Day -1
Informed consent	X
Demographics	X
Medical history	X
Ophthalmological history	X
Prior and concomitant medications	X
Height, weight, and BMI[a]	X
Vital signs[b]	X
Ophthalmologic examination[c]	X
Physical examination[d]	X
Standard 12-lead electrocardiogram (ECG)[e]	X
CFTR genotype[f]	X
Sweat chloride[g]	X
Spirometry[h]	X
Urinalysis[i]	X
Serum FSH (postmenopausal female subjects only)	X
Serum β-HCG (all female subjects)	X
Serum chemistry[j]	X
Hematology[j]	X
Coagulation[j]	X
Activity tracking via actigraphy	Continuous for 1 week during the Screening Period
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit

[a] Height and weight will be measured with shoes off.

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

[c] For all subjects <18 years of age, except for those who have had bilateral lens removal, an ophthalmologic examination will be conducted by a licensed ophthalmologist or optometrist. If there is documentation that an examination meeting protocol criteria was conducted within 3 months before the Screening Visit, the ophthalmologic examination does not need to be performed during the Screening Period.

[d] The physical examination includes an assessment of all body systems.

[e] The ECG will be performed before any other procedures that may affect heart rate (e.g., blood draws).

[f] *CFTR* genotyping will be performed to determine that the subject is homozygous for the *F508del-CFTR* mutation. If homozygous *F508del-CFTR* genotype is documented in the subject's medical records, *CFTR* genotyping during screening is not required.

[g] A sweat chloride assessment at the Screening Visit is required only if the subject does not have a sweat chloride value documented in their medical history that meets the study eligibility criteria.

[h] Spirometry will be assessed before the cardiopulmonary exercise test.

[i] If urinalysis results are positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be performed.

[j] Blood samples will be collected for clinical laboratory assessments after a fast of at least 4 hours.

Table 3-2 Study 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 the 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] The 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 3-2 Study 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. Details are provided in Section 10.2.

[l] All subjects will be reminded of the standard exercise recommendations for patients with CF.

[redacted]

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5 INTRODUCTION

5.1 Study Rationale

This study is designed to evaluate the effect of lumacaftor/ivacaftor (LUM/IVA) combination therapy on exercise tolerance in subjects with cystic fibrosis (CF). Patients with CF exhibit exercise intolerance, and although pulmonary symptoms are partially responsible, cardiovascular or myopathic factors are believed to be the major limitation in patients with milder disease.[1,2]

Exercise capacity, as measured by maximal oxygen consumption (VO_{2max}) during cardiopulmonary exercise tests (CPETs), has been demonstrated to be a significant predictor of mortality in patients with CF.[3,4] A randomized crossover study[5] and published case series[6,7] suggest that ivacaftor (IVA) may improve VO_{2max} and other measures of exercise capacity. These findings may be independent of improvements in forced expiratory volume in 1 second (FEV_1) previously demonstrated with ivacaftor. To date, there has been no prospective randomized evaluation of LUM/IVA effects on exercise capacity as measured by CPET.

In this study, the CPET will be used to assess improvements in exercise tolerance, as measured by VO_{2max}, after up to 24 weeks of LUM/IVA therapy. The study population will be patients with CF who are 12 years of age and older and are homozygous for the *F508del-CFTR* mutation.

[redacted]

5.2 Background

Cystic fibrosis is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality, and at present, there is no cure. Cystic fibrosis affects approximately 70,000 individuals worldwide,[8] with approximately 30,000 individuals in the US,[9] 36,000 individuals in the European Union (EU),[10] 3,800 individuals in Canada,[11] and 3,000 individuals in Australia.[12] The incidence and prevalence of CF varies between racial groups. For example, CF is considerably more common in the Caucasian populations of North America and Europe than in Asian and African populations.[9,10] Based on the size of the population, CF qualifies as an orphan disease.[13,14] Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is approximately 40 years.[9,15,16] Although the disease affects multiple organs, progressive loss of lung function is the leading cause of mortality.[17]

Cystic fibrosis is caused by a defect in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), an epithelial chloride (Cl^-) ion channel activated by cyclic AMP-dependent protein kinase A (PKA) that is responsible for aiding in the regulation of

salt and water absorption and secretion in various tissues.[18] This function is defective in patients with CF due to loss of cell surface expression and/or function of CFTR.

More than 1900 mutations in the *CFTR* gene have been identified.[19] The most prevalent mutation is an in-frame deletion in the *CFTR* gene resulting in a loss of phenylalanine at position 508 in the wild-type CFTR protein (*F508del-CFTR*).[20] In the US, almost 87% of patients with CF have at least 1 copy of the *F508del-CFTR* mutation, and about 47% have 2 copies.[21] In the EU, approximately 85% of patients with CF have at least 1 copy of the *F508del-CFTR* mutation, and approximately 38.7% of patients with CF in the United Kingdom have 2 copies.[22] The *F508del-CFTR* mutation interferes with the ability of the CFTR protein to reach and remain at the cell surface, as well as to open and close, resulting in decreased Cl^- transport.[23,24] Because of the near-complete loss of CFTR chloride transport, the *F508del/F508del* genotype is typically associated with a severe form of CF, characterized by a rapid rate of lung function decline, colonization with *Pseudomonas aeruginosa*, a high incidence of pancreatic insufficiency, and reduced life expectancy.[25,26,27,28]

Based on the understanding of the molecular defects caused by *CFTR* mutations, 2 complementary approaches have been developed to address the decreased quantity and/or function of CFTR in order to enhance chloride transport in patients with CF. The first approach is to increase the quantity of CFTR delivered to the cell surface using small molecules known as CFTR correctors. The second approach is to increase the channel gating activity of CFTR at the cell surface using small molecules known as CFTR potentiators. One or both of these mechanisms may be necessary depending on the specific mutation. Because the channel gating activity of CFTR delivered to the cell surface by CFTR correctors can be enhanced by CFTR potentiators, together, CFTR correctors and potentiators provide complementary therapeutic approaches to improve chloride transport.

Lumacaftor (LUM) is a CFTR corrector that improves the processing and trafficking of the F508del-CFTR protein, resulting in an increase in the quantity of F508del-CFTR protein at the cell surface. IVA increases the channel-open probability of the F508del-CFTR protein delivered to the cell surface by LUM, thereby enhancing total chloride transport. In the absence of LUM, there is very little F508del-CFTR protein at the cell surface for IVA to potentiate. The combined effect of LUM and IVA is increased quantity and function of F508del-CFTR at the cell surface.

LUM and IVA in combination is the first medicine designed to treat the underlying molecular defect and enhance the function of CFTR in patients homozygous for *F508del*. The LUM/IVA development program targets patients with CF who have the *F508del* mutation, the most common mutation in the *CFTR* gene. The program is designed to support the hypothesis that an oral chronic treatment restoring CFTR function can lead to improved pulmonary and extrapulmonary manifestations of CF, prevent progressive lung damage, and ultimately prolong survival.

Details about the LUM/IVA development program can be found in the Investigator's Brochure.[29]

6 STUDY OBJECTIVES

6.1 Primary Objective

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

6.2 Secondary Objectives

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

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Percentage change from baseline in VO_{2max} during cardiopulmonary exercise testing (CPET) at Week 24

7.2 Secondary Endpoints

Key Secondary Endpoint

- Change from baseline in exercise duration during CPET at Week 24

Other Secondary Endpoints

- Change from baseline in oxygen consumption (VO_2) at anaerobic threshold (AT) (the exercise intensity at which lactate starts to accumulate) at Week 24
- Change from baseline in functional VO_2 gain at Week 24
- Change from baseline in the pulmonary ventilation (VE) versus carbon dioxide production (VCO_2) slope at Week 24
- Change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at Week 24
- Change from baseline in body mass index (BMI) at Week 24
    - Change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score at Week 24
    - Change from baseline in overall Patient Health Questionnaire (PHQ-8) and Generalized Anxiety Disorder (GAD-7) scores at Week 24
- Change from baseline in physical activity as determined by actigraphy at Week 24
- Change from baseline in duration of sleep time and change in sleep quality during the night at Week 24
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values (serum chemistry and hematology), vital signs, and ophthalmologic examinations (for subjects under 18 years of age only).

[redacted]

8 STUDY DESIGN

8.1 Overview of Study Design

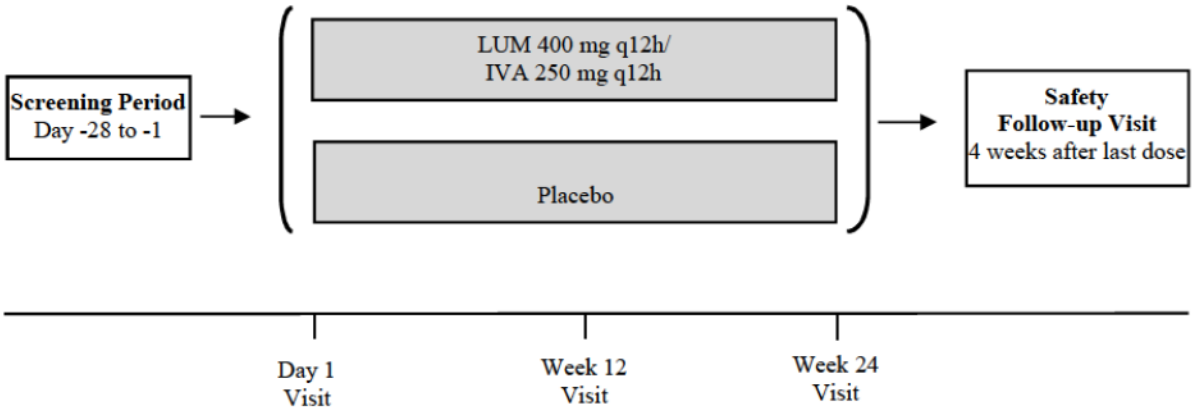
This is a Phase 4, randomized, double-blind, placebo-controlled, parallel-group study in subjects aged 12 years and older with CF who are homozygous for the *F508del-CFTR* mutation. This study is designed to evaluate the effect of LUM/IVA on exercise tolerance.

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 8-1 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]

Figure 8-1 Schematic View of the Study Design



8.1.1 Screening

Screening Visit assessments are listed in Table 3-1.

Screening will occur within 28 days before administration of study drug. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from each subject.

To prepare for study participation, subjects will be instructed on the study restrictions (Section 9.3).

Subjects who do not meet the eligibility criteria may not be rescreened, with the following exceptions, all of which require medical monitor approval:

- Subjects who met all eligibility criteria, but had an intercurrent illness (e.g., upper respiratory infection with fever) in the 5 days before the first study drug dose that was properly evaluated and that resolved fully
- Subjects who met all eligibility criteria, but were not able to obtain required documentation within the allotted screening window
- Subjects who met all eligibility criteria, but transiently (for personal reasons) were unable to commit to all study procedures
- Subjects who met all eligibility criteria, but were not randomized for administrative reasons (e.g., interactive web response system [IWRS] was temporarily inaccessible or nonfunctional, or study drug was not available at the study site)

Any subject granted approval by the medical monitor for any of the exceptions listed above may have the screening window extended by 1 week before needing to undergo any rescreening assessments. If more than 35 days have elapsed from screening before first dose of study drug, all screening assessments need to be repeated. Repetition of any screening assessment that did not meet eligibility criteria is not permitted, unless there is clear evidence

of a laboratory error (e.g., hemolysis of sample). In all cases, the medical monitor must authorize retesting.

8.1.2 Treatment Period

Treatment Period assessments are listed in Table 3-2.

The Treatment Period will be conducted as described previously in Section 8.1. Dosing details are given in Section 10.2.

Subjects who prematurely discontinue study drug treatment will remain in the study from the time of discontinuation through the Safety Follow-up Visit, as described in Section 8.1.4.

8.1.3 Follow-up

Subjects will have a Safety Follow-up Visit 4 weeks (± 7 days) after the last study drug dose. Safety Follow-up Visit assessments are listed in Table 3-2. When the Safety Follow-up Visit is complete, the subject has completed the study.

8.1.4 Early Termination of Treatment

If the subject prematurely discontinues study drug, an Early Termination of Treatment (ETT) Visit will be scheduled as soon as possible after the subject decides to terminate study drug. Subjects who prematurely discontinue study drug will also complete the Safety Follow-up Visit, approximately 4 weeks ± 7 days after their last dose of study drug. The assessments performed at the Safety Follow-up Visit are listed in Table 3-2.

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.

If the subject withdraws consent for the study, no further evaluations will be performed, and no additional data will be collected. Vertex Pharmaceuticals Incorporated (Vertex) may retain and continue to use any data collected before such withdrawal of consent.

8.2 Rationale for Study Design and Study Drug Regimens

8.2.1 Study Design

This study is designed to evaluate the effect of LUM/IVA therapy on exercise tolerance in subjects with CF after up to 24 weeks of LUM/IVA therapy. CPETs will be used to assess improvements in exercise tolerance, as measured by VO_{2max}.

The use of a placebo control group is deemed necessary because exercise tolerance can be affected by a number of factors, including activity level, and subject activity may increase as a result of being involved in an exercise tolerance study.

This study will only enroll subjects who have not previously been exposed to LUM or IVA, and all subjects will continue their normal, stable treatment for CF throughout the study.

The study population will be subjects with CF who are 12 years of age and older and are homozygous for the *F508del-CFTR* mutation. Efficacy, safety, and pharmacokinetic profiles for LUM/IVA therapy were established in subjects 12 years of age and older with CF homozygous for the *F508del-CFTR* mutation in Studies VX12-809-103 (Study 103) and

VX12-809-104 (Study 104). Furthermore, this is the population for which LUM/IVA treatment has been approved in Europe and in the US.

8.2.2 Study Drug Dose and Duration

The dosing regimen for LUM/IVA (LUM 400 mg/IVA 250 mg every 12 hours [q12h]) was selected on the basis of acceptable tolerability and favorable exposure observed in previous clinical studies of LUM/IVA,[29] and because it has been approved in Europe and in the US for the treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation.[30,31]

8.2.3 Rationale for Study Assessments

CPET: Maximal cardiopulmonary exercise testing that incorporates measurements of gas exchange provides precise measurements of exercise tolerance. This assessment provides several parameters of exercise tolerance and aerobic fitness including VO_2, functional VO_2 gain, VCO_2, AT, and VE. Functional VO_2 gain relates oxygen uptake to total ventilation during exercise and is an index of cardiopulmonary reserve. The VE versus VCO_2 slope is a measure of ventilatory efficiency. The AT is the exercise intensity at which lactate starts to accumulate.

Spirometry: Because lung disease is the major cause of morbidity and mortality for patients with CF, FEV_1, as measured by spirometry, is the most widely implemented standardized assessment to evaluate lung function in CF.

Actigraphy: Exercise tolerance can be affected by a number of factors, including activity level. In this study, subjects' activity levels will be monitored by actigraphy to determine whether subjects' activity increased with LUM/IVA treatment and to examine the relationship between physical activity and changes in exercise tolerance. Actigraphy will also be used to capture sleep/wake data, which reflect both functional and physiological health of subjects. The actigraph device can capture continuous sleep/wake data over a long period of time, is a cost-effective and minimally invasive in-home alternative to other methods to measure these behaviors (e.g., polysomnography), and offers a level of accuracy and reliability that cannot be achieved through subjective reports.

BMI: Malnutrition is common in patients with CF because of increased energy expenditures due to lung disease and fat malabsorption. Improved nutritional status, defined as an increase in weight and/or BMI, is an endpoint that has been used in previous clinical studies of LUM/IVA therapy (Studies 103 and 104).

Questionnaires pertaining to quality of life, depression, and anxiety—the CFQ-R, PHQ-R, and GAD-7: The CFQ-R is a validated CF-specific instrument that measures the health-related quality of life of patients with CF.[32,33,34] The adolescent/adult version, the parent/caregiver version, and the child version measure quality-of-life domains including respiratory symptoms, digestive symptoms, emotion, and health perception. Furthermore, the CFQ-R has been evaluated in clinical studies involving therapies for CF lung disease.[35,36,37] Linguistically validated versions of the CFQ-R[38,39] are available, thereby allowing consistent interpretation of the results in this global study.

Several recent studies have documented the high rates of symptoms of depression and anxiety in patients with CF.[40-43] The PHQ-8 is used to assess the presence of depressive symptoms in non-depression studies via 8 items that correspond to diagnostic criteria for major depressive disorder and depression severity. Various levels in the resulting score correspond to various levels of depression severity. The GAD-7 assesses the presence of anxiety symptoms via 7 items that are based on the symptom criteria for generalized anxiety disorder

[redacted]

9 STUDY POPULATION

Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are enrolled.

9.1 Inclusion Criteria

Subjects who meet all of the following inclusion criteria will be eligible:

1. Subject (or their legally appointed and authorized representative) will sign and date an informed consent form (ICF), and where appropriate, assent form.
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Subjects (male and female) will be at least 12 years old on the date of informed consent.
4. Homozygous for the *F508del-CFTR* mutation (as documented in the subject's medical records or from genotyping performed during screening).

5. Confirmed diagnosis of CF[44] defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis, as documented:
   - in the subject's medical records **OR**
   - from sweat chloride test result obtained during screening (to be conducted only if the subject does not have a sweat chloride test result in the medical records).
6. Stable CF disease as judged by the investigator.
7. FEV_1 at least 40% and not greater than 90% of predicted.
8. Willing to remain on a stable CF medication regimen through the Safety Follow-up Visit.

9.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will **not** be eligible:

1. History of any comorbidity that might confound the results of the study, interfere with the use of CPET as an assessment, or pose an additional risk in administering study drug to the subject. For example:
   - history of cirrhosis with portal hypertension.
   - inability to exercise.
   - requiring additional oxygen with exercise.
2. Any of the following abnormal laboratory values at Screening:
   - hemoglobin <10 g/dL.
   - any 2 or more of the following: aspartate aminotransferase (AST) ≥3 × upper limit of normal (ULN), alanine aminotransferase (ALT) ≥3 × ULN, gamma-glutamyl transpeptidase (GGT) ≥3 × ULN, or alkaline phosphatase (ALP) ≥3 × ULN.
   - total bilirubin ≥2 × ULN.
   - AST or ALT ≥5 × ULN.
   - glomerular filtration rate ≤50 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease Study Equation)[45,46] for subjects ≥18 years of age and ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation)[47] for subjects aged 12 to 17 years (inclusive).
3. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1.
4. A 12-lead electrocardiogram (ECG) demonstrating QTc >450 msec at Screening. If QTc exceeds 450 msec for the screening ECG, the ECG will be repeated 2 more times during the Screening Period, and the average of the 3 QTc values will be used to determine the subject's eligibility.

5. History of cardiac arrhythmia, ischemic heart disease, congestive heart failure, or other clinically significant cardiac condition, or medical condition requiring chronic use of a beta blocker, non-dihydropyridine calcium channel blocker, or other cardiac medication known to affect exercise tolerance.
6. History of solid organ or hematological transplantation.
7. For subjects under 18 years of age at Screening, except those who have had bilateral lens removal: history or evidence of cataract, lens opacity, Y-suture, or lamellar rings determined to be clinically significant by the ophthalmologist or optometrist during the ophthalmologic examination during the Screening Period. (The ophthalmologic examination does not need to be performed at Screening if there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the Screening Visit.)
8. Using or expected to require any concomitant medication that is prohibited in this study, as discussed in Section 9.4.1.
9. History of alcohol or drug abuse, as deemed by the investigator, in the past year, including but not limited to cannabis, cocaine, and opiates.
10. Participation in an investigational drug study within 30 days before the Screening Visit.
11. Any previous exposure to LUM or IVA.
12. Pregnant or nursing females (females of childbearing potential must have a negative pregnancy test at Screening and Day 1); males with a female partner who is pregnant or nursing.
13. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study. An adult (aged 18 years or older) who is a relative of a study staff member may be randomized in the study provided that
    - the adult lives independently of and does not reside with the study staff member.
    - the adult participates in the study at a site other than the site at which the family member is employed.
14. Colonization with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*). For subjects who have had a history of a positive culture in the past, the investigator could be guided by the following suggested criteria for a subject to be considered free of colonization:
    - The subject should have had 2 respiratory tract cultures negative for these organisms within the past 12 months, with no subsequent positive cultures.
    - These 2 respiratory tract cultures should have been separated by at least 3 months.
    - One of these 2 respiratory tract cultures should have been obtained within the past 6 months.

9.3 Study Restrictions

Prohibited medications and certain foods are not allowed (Screening Period through Week 24) as summarized in Table 9-1.

A nonexhaustive list of study prohibitions and cautions for food and medication will be provided.

Table 9-1 Study Restrictions

	Study Period	
Restricted Medication/Food[a]	**Screening Period**	**Treatment Period**
Strong CYP3A inducers	None allowed within 14 days before the first dose of study drug	None allowed
Strong CYP3A inhibitors	None allowed within 14 days before the first dose of study drug	Use with caution

Note: The use of restricted medication in subjects with a medical need will be addressed on a case-by-case basis with the medical monitor or authorized designee.

[a] See Section 9.4 for guidance for concomitant medications.

9.4 Prior and Concomitant Medications

9.4.1 Prohibited Medications

Prohibited medications as described in Table 9-1 are not allowed while subjects are receiving study drug.

The use of cytochrome P450 (CYP) 3A substrates is not prohibited, but investigators need to be aware that LUM appears to be a strong inducer of this CYP isoenzyme. Therefore, the efficacy of drugs extensively metabolized by this isoenzyme may be affected. Each investigator should evaluate the benefit/risk ratio of using such drugs with LUM during this study. Investigators should discuss any concerns regarding the use of CYP3A substrates during this study with the Vertex medical monitor or authorized designee.

The use of CYP2C and CYP2B6 substrates are not prohibited, but investigators need to be aware that LUM has been shown in vitro to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19; inhibition of CYP2C8 and CYP2C9 has also been observed in vitro. Additionally, in vitro studies suggest that IVA may inhibit CYP2C9. Therefore, concomitant use of LUM in combination with IVA with CYP2B6, CYP2C8, CYP2C9, and CYP2C19 substrates may alter the exposure of these substrates.

Each investigator should evaluate the benefit-risk ratio of using such drugs with LUM and IVA during this study and discuss the use of these substrates during this study with the medical monitor or authorized designee.

The use of strong inhibitors of CYP3A is not prohibited, but investigators need to be aware that a strong inhibitor of CYP3A has been shown to increase the exposure of IVA when given in combination with LUM; however, due to the induction effect of LUM, the net exposure of IVA is not expected to exceed previous experiences with IVA monotherapy. Subjects who are using strong CYP3A inhibitors do not require study drug interruption.

However, if they interrupt study drug for more than 72 hours, study drug resumption requires medical monitor discussion and approval. Each investigator should evaluate the benefit-risk ratio of using such drugs with LUM and IVA during this study and discuss the use of these strong inhibitors of CYP3A during this study with the medical monitor or authorized designee.

A nonexhaustive study prohibitions and cautions list for food and medications will be provided.

9.4.2 Prior and Concomitant Medications

Information regarding all prior and concomitant medications, including the subject's CF medications, other medications, and herbal and naturopathic remedies, administered from 30 days before the Screening Period through the Safety Follow-up Visit will be recorded in each subject's source documents and electronic case report form (eCRF).

It is recommended that subjects remain on a stable medication regimen for their CF from 4 weeks before Day 1 through the Safety Follow-up Visit. Stable medication regimen is defined as the current medication regimen for CF that subjects have been following for at least 4 weeks before Day 1.

9.5 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. If a subject has discontinued study drug treatment, the subject will continue to be followed, provided the subject has not withdrawn consent.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return for a Safety Follow-up Visit, if applicable (see Section 8.1.4), and follow up with the subject regarding any unresolved AEs.

If the subject withdraws consent for the study, no further evaluations will be performed and no additional data will be collected. Vertex may retain and continue to use any data collected before such withdrawal of consent.

Specific instructions for interruption for elevated liver function test (LFT) levels are provided in Section 11.5.3.

9.6 Replacement of Subjects

Subjects who withdraw or are withdrawn during the Treatment Period will not be replaced.

10 STUDY DRUG ADMINISTRATION AND MANAGEMENT

10.1 Preparation and Dispensing

Study drug (LUM/IVA or placebo) may be dispensed only under the supervision of the investigator or an authorized designee and only for administration to the study subjects.

10.2 Administration

Study drug will be administered orally, 2 times a day, with food. Study drug should be administered within 30 minutes of consuming fat-containing food such as a standard CF high-fat, high-calorie meal or snack according to the following guidelines:

1. Study drug will be administered q12h (± 2 hours).
2. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. The meal or snack will be provided by the site for the morning dose of study drug.
3. If a subject's scheduled visit is to occur in the afternoon, the following guidelines must be used:
    - If the dose in the clinic will be within 6 hours of the subject's scheduled morning dose, the subject should withhold their morning dose of study drug and the morning dose will be administered in the clinic.
    - If the dose in the clinic will be more than 6 hours after the subject's scheduled morning dose, the subject should take the morning dose at home and the evening dose will be administered in the clinic. In this event, all assessments will be collected relative to the evening dose.
4. For visits after the Day 1 Visit, subjects will be instructed to bring all used and unused study drug to the site; study drug will be dispensed at each visit, as appropriate.
5. At the Week 24 Visit, the morning dose of study drug will NOT be administered. The last dose of study drug will be the evening dose administered the day before the Week 24 Visit.

10.3 Missed Doses

If subjects miss a dose and recall the missed dose within 6 hours, they should take their dose with food. If more than 6 hours have elapsed after their usual dosing time, they should skip that dose and resume their normal schedule for the following dose. For example:

- If the morning dose of study drug should have been taken at approximately 08:00, and the subject remembers at 12:00 that he/she forgot to take the morning dose, the subject should take the dose with food as soon as possible. The subject should then take the evening dose at the usual time, approximately 20:00.
- If the morning dose of study drug should have been taken at approximately 08:00, and the subject does not remember until after 14:00, the subject should resume dosing with the evening dose at approximately 20:00.

10.4 Study Drug Interruption

If study drug dosing must be interrupted for more than 72 hours, the medical monitor must be notified. In these instances, study drug dosing may only resume after approval by the medical monitor. Specific instructions for interruption for elevated LFT levels are provided in Section 11.5.3.

10.5 Method of Assigning Subjects to Treatment Groups

An interactive web or voice response system (IXRS) will be used to assign subjects to treatment. The randomization code will be produced by Vertex Biostatistics or a qualified randomization vendor. The Vertex study biostatistician will review and approve the production of the final randomization list, which will be reviewed and approved by a designated unblinded biostatistician who is not a member of the study team.

10.6 Packaging and Labeling

Study drug tablets will be supplied in blister cards by Vertex. Study drug cards will be provided and replaced via the IWRS. A detailed study drug dispensation plan will be provided in the Pharmacy Manual.

Study drug labeling will be in compliance with applicable local and national regulations.

10.7 Study Drug Supply, Storage, and Handling

Table 10-1 provides the study drug information. The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for via the drug accountability forms as instructed by Vertex.

Detailed instructions regarding the storage, handling, and dispensation of the study drug will be provided in the Pharmacy Manual.

Table 10-1 Study Drug

Drug Name	Formulation/ Route	Packaging (Formulation Strength)	Storage Condition
Lumacaftor/ivacaftor (fixed-dose)	Fixed-dose tablet/ Oral	Supplied as 200-mg lumacaftor/125-mg ivacaftor tablets	Store at ≤30°C (86°F)
Placebo (appearance matched to lumacaftor/ivacaftor tablets)	Tablet/Oral	No active drug	Store at ≤30°C (86°F)

10.8 Drug Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of study drug received, study drug dispensed to the subjects, and study drug returned by the subjects. Subjects will be instructed to return all used and unused materials associated with the study drug to the site. These materials will be retained at the site according to instructions provided by Vertex or its designee until inventoried by the study monitor. The study monitor will review study drug records and inventory throughout the study.

10.9 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subjects until the study monitor has performed drug accountability. At the end of the study, the study

monitor will provide instructions as to the disposition of any unused investigational product. If the study monitor authorizes destruction at the study site, the investigator will ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Vertex. Destruction will be adequately documented.

10.10 Compliance

For study drug doses administered during study visits, doses will be administered under the direct supervision of the investigator or designee.

For study drug doses administered outside of study visits, drug accountability will be assessed at each visit by counting returned dosage units. Discrepancies will be discussed with the subject and recorded in the source documents. If a subject demonstrates continued noncompliance of study drug dosing despite educational efforts, the investigator will contact the medical monitor to discuss withdrawing the subject from the study.

10.11 Blinding and Unblinding

This is a double-blind study.

10.11.1 Blinding

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 their fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel for whom this information is important 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
- Unblinded personnel from Vertex Data Management IWRS management
- Unblinded personnel from Vertex Clinical Supply Chain

The Vertex medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time.

Subjects and their parents/caregivers will not be informed of their study-related efficacy results during the study, regardless of whether or not the subject prematurely discontinues treatment.

10.11.2 Unblinding

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

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

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

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

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor will be notified within 24 hours of the unblinding event. The reason and the date of the unblinding will be documented clearly in the subject's study file. Information about the treatment assignment obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with the sponsor (Vertex), contract research organization (CRO), or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs (Section 13.1.2.1), and if so, submit an SAE report to Vertex GPS or designee, per Section 13.1.2.3.

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.

11 ASSESSMENTS

11.1 Timing of Assessments

The timing of assessments is shown in Table 3-1 and Table 3-2.

11.2 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, and weight.

11.3 Pharmacokinetics

Not applicable.

11.4 Efficacy

Subjects and their parents/caregivers will not be informed of their study-related efficacy results during the study, regardless of whether or not the subject prematurely discontinues treatment.

11.4.1 Cardiopulmonary Exercise Testing

The CPET will be assessed at the time points noted in Table 3-2.The CPET will be conducted using the Godfrey protocol[48], which has been used in a number of studies of exercise tolerance in patients with CF. According to the Godfrey protocol, the CPET will be conducted using a cycle that ramps resistance over time. The CPET includes pulse oximetry.

11.4.2 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines[49] at the time points noted in Table 3-1 and Table 3-2 according to the additional guidelines that follow.

Pre-bronchodilator spirometry is defined as spirometry testing performed for subjects who have

- withheld their short-acting bronchodilators (e.g., albuterol) or anticholinergic (e.g., Atrovent®) for more than 4 hours before the spirometry assessment;
- withheld their long-acting bronchodilator (e.g., salmeterol) for more than 12 hours before the spirometry assessment; and
- withheld their once-daily, long-acting bronchodilator (e.g., tiotropium bromide [Spiriva®]) for more than 24 hours before the spirometry assessment.

All spirometry assessments should be performed post-bronchodilator (unless the subject is not using a bronchodilator on a regular basis). During the Treatment Period, spirometry assessments must be performed before administration of study drug. At visits that include both spirometry and the CPET, spirometry will be assessed before the CPET.

Each spirometry assessment will be recorded in the source documents as pre-bronchodilator or post-bronchodilator.

All sites will be provided with spirometers to be used for all study assessment.

The parameters listed below will be normalized using the standards of Wang et al.[50] (for female subjects aged 12 to 15 years [inclusive] and male subjects aged 12 to 17 years [inclusive]) or Hankinson et al.[51] (for female subjects aged 16 years and older and male subjects aged 18 years and older).

- FEV_1 (L)
- Forced vital capacity (FVC) (L)
- FEV_1/FVC (ratio)
- Forced expiratory flow ($FEF_{25\%-75\%}$) (L/s)

11.4.3 Actigraphy

Subjects will be provided with a wrist-worn actigraphy device at the Screening Visit and will wear the device through the Week 24 Visit, as specified in Table 3-1 and Table 3-2. The device is non-invasive, similar to a wrist watch. The subjects will wear the device on the wrist of their nondominant hand and can wear it 24 hours per day. The device will continuously collect data about daily activities and sleep duration and quality. Subjects will bring in the device during study visits for the site staff to upload the data from the device. Actigraphy data will be centrally read. The device will be returned to the study site at the subject's final study visit.

11.4.4 Height, Weight, and BMI

Height and weight will be measured with shoes off at time points noted in Table 3-1 and Table 3-2. 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.

As children gain weight and height as part of normal growth, adjustment for age and sex is necessary to assess changes in nutritional status in a population of boys and girls at varying stages of growth. To evaluate the effect of LUM/IVA on growth and nutrition adjusted for age and sex, weight-for-age, BMI-for-age, BMI-for-age z-scores, and height-for-age z-scores will be determined. Height and weight will be collected at the study visits indicated in the schedule of assessments.

11.4.5 Cystic Fibrosis Questionnaire – Revised

CFQ-R will be completed at the time points noted in Table 3-2. 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.

The CFQ-R will be completed before the start of any other assessments. Subjects who are 12 or 13 years of age at the Screening Visit will complete the CFQ-R Child version themselves for the entire study duration, regardless of whether the subject turns 14 years of age during the study. Subjects 14 years of age and older at the Screening Visit will complete the Adolescent/Adult version of the questionnaire themselves at all visits. The questionnaires provide information about demographics; general quality of life, school, work, or daily activities; and symptom difficulties (pertaining to CF). Copies of the CFQ-R used in this study will be provided. Validated translations[38,39] of the CFQ-R will be provided for participating centers in non-English-speaking countries.

11.4.6 Patient Health Questionnaire (PHQ-8)

The PHQ-8 will be completed at the time points noted in Table 3-2. 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.

The PHQ-8 provides information about 8 items that correspond to diagnostic criteria for major depressive disorder and depression severity.

11.4.7 Generalized Anxiety Disorder (GAD-7)

The GAD-7 will be completed at the time points noted in Table 3-2. 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.

The GAD-7 provides information about 7 items that are based on the symptom criteria for generalized anxiety disorder.

[redacted]

11.5 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, ophthalmologic examinations (for subjects under 18 years of age only), and physical examinations (PEs). Spirometry data will also be used as safety-supporting data.

11.5.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with ICH GCP guidelines. Section 13.1 outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting AEs. A separate document that details AE CRF completion guidelines for investigators as well as training will be provided.

11.5.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory. At the Screening Visit, blood specimens will be collected for safety laboratory tests after a fast of at least 4 hours. Fasting is not required at other time points. On Day 1, blood samples will be collected before the first dose of the study drug. At all other scheduled visits, these samples will be collected at any time during the visit.

Blood and urine samples for clinical laboratory assessments will be collected as shown in Table 3-1 and Table 3-2. Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

The safety laboratory test panels are shown in Table 11-1.

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis (at Screening only)[a]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen	Erythrocytes	Nitrite
Creatinine	Mean corpuscular volume	Urobilinogen
Sodium	Platelets	Urine protein
Potassium	Reticulocytes (absolute)	pH
Calcium	Leukocytes	Urine blood
Chloride	Differential (absolute and percent):	Specific gravity
Magnesium	Eosinophils	Urine ketones
Bicarbonate	Basophils	Urine bilirubin
Phosphate	Neutrophils	Urine glucose
Bilirubin, direct bilirubin	Lymphocytes	
ALP	Monocytes	
AST	**Coagulation (at Screening only)**	
ALT	Activated partial thromboplastin time	
Amylase	Prothrombin time	
Lactate dehydrogenase	Prothrombin time International Normalized Ratio	
Lipase		
GGT		
Protein		
Albumin		
Creatine kinase		

Note: Screening Visit blood draws will be done after a fast of at least 4 hours. All subsequent blood draws do not require fasting.

[a] If urinalysis results are positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be performed and results provided for leukocytes, erythrocytes, crystals, bacteria, and casts.

Additional tests at screening: The following additional tests will be performed during screening to assess eligibility:

- Serum beta-human chorionic gonadotropin (β-HCG) for all female subjects
- Serum follicle-stimulating hormone for suspected postmenopausal female subjects only. Levels will be within the laboratories range for postmenopausal for subjects to be considered of non-childbearing potential.
- CF genotyping will be performed if homozygous *F508del-CFTR* is not documented in the subject's medical records.

Pregnancy Testing for Female Subjects of Childbearing Potential: Childbearing potential is defined in Section 11.5.7.1. Pregnancy testing will be conducted every 4 weeks starting on Day 1 (before the first dose of study drug) and continuing through the Safety Follow-up Visit with a urine β-HCG test. 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.

If a urine pregnancy test is positive, all study drug dosing will stop and the pregnancy will be confirmed with a serum β-HCG test. If confirmed, the pregnancy will be reported and study

drug dosing will be permanently discontinued, as discussed in Section 8.1.4. If a pregnancy test is positive, the procedures outlined in Section 11.5.7.2 will be followed.

Additional Evaluations: Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate.

For purposes of study conduct, only laboratory tests done in the central laboratory may be used. Local laboratories may be used at the discretion of the local investigator for management of urgent medical issues. If a local laboratory test value is found to be abnormal and clinically significant, it will be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. If it is not possible to send a timely specimen to the central laboratory (e.g., the subject was hospitalized elsewhere), the investigator may base the assessment of an AE on the local laboratory value.

11.5.3 Elevation of Liver Function Test Parameters

Mandatory Liver Function Testing

Liver function testing (ALT, AST, GGT, ALP, and total bilirubin) must be performed while subjects are receiving study drug treatment (Table 3-2). These blood samples will be processed and shipped immediately per the Laboratory Manual.

It is strongly recommended that subjects with new treatment-emergent ALT or AST elevations of >3 × ULN and clinical symptoms be followed closely, including repeat confirmatory testing performed by the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT and AST levels, as clinically indicated.

If a subject cannot return to the site for liver function testing, a local laboratory may be used. Elevations in LFTs (as indicated above) at the local laboratory must be reported immediately to the medical monitor **and** the subject must have the tests repeated and sent to the central laboratory as soon as possible (ideally within 48 to 72 hours).

Study Drug Interruption

Study drug administration **must be interrupted** immediately, and the medical monitor must be notified if any of the following criteria is met:

- ALT or AST >8 × ULN
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN, in association with total bilirubin >2 × ULN and/or clinical jaundice

A thorough investigation of potential causes should be conducted, and the subject should be followed closely for clinical progression.

If no convincing alternative etiology (e.g., acetaminophen use, viral hepatitis, or alcohol ingestion) for the elevated transaminases is identified, regardless of whether ALT or AST levels have improved, study drug treatment must be discontinued, in consultation with the Vertex medical monitor or authorized designee. Subjects in whom treatment is discontinued for elevated transaminases should have their transaminases monitored closely until levels normalize or return to baseline.

Resumption of Study Drug

If a convincing alternative etiology is identified for the elevated transaminases (ALT, AST, and total bilirubin), study drug may be resumed when transaminases return to baseline or are ≤2 × ULN, whichever is higher. Approval of the Vertex medical monitor or designee is required before resumption of study drug. Upon resumption of study drug, transaminases will be assessed weekly for 4 weeks. If a protocol-defined transaminase elevation occurs within 4 weeks of rechallenge with the study drug, then the study drug must be discontinued, regardless of the presumed etiology.

11.5.4 Physical Examinations and Vital Signs

A PE of all body systems and vital signs assessment will be performed at the Screening Visit and select study visits (see Table 3-1 and Table 3-2). At other visits, symptom-directed PEs and symptom-directed vital sign assessments can be performed at the discretion of the investigator or healthcare provider.

A PE includes a review of the following systems: head/neck/thyroid; eyes/ears/nose/throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in PEs will be reported as AEs.

Vital signs include blood pressure (systolic and diastolic), temperature (oral), pulse rate, and respiration rate. These will be assessed after the subject has been seated for at least 5 minutes and before administration of study drug (if applicable). Blood pressure will be taken using a manual sphygmomanometer.

11.5.5 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout at Screening as shown in Table 3-1. Additional standard 12-lead ECGs will be performed at any other time if clinically indicated. The ECG will be performed before any other procedures that may affect heart rate, such as blood draws.

The ECG traces will be manually read at the study site at the Screening Visit. A printout of the ECG traces will be made for safety review by the investigator and maintained with source documentation. Clinically significant ECG abnormalities occurring during the study through the Safety Follow-up Visit will be recorded as AEs.

11.5.6 Ophthalmologic Examinations and History

All subjects who are <18 years of age at the Screening Visit, except those who have had bilateral lens removal, will undergo an ophthalmologic examination at the Screening Visit and at 1 of the following visits: the Week 24 Visit, the ETT Visit, or the Safety Follow-up Visit. These examinations will include:

- measurement of best corrected distance visual acuity of each eye
- measurement of lens refracting power (e.g., autorefractor or ophthalmoscopy streak following cycloplegia)

- pharmacologically dilated examination of the lens with a slit lamp
- presence of Y-suture or lamellar rings

These examinations will be conducted by a licensed ophthalmologist or optometrist. The screening ophthalmologic examination will be completed and the results reviewed before enrollment. If a cataract, lens opacity, Y-suture, or lamellar rings are identified and determined to be clinically significant by the ophthalmologist or optometrist at the Screening Examination, the subject will not be enrolled. If there is documentation that an examination meeting protocol criteria was conducted within the 3 months before the Screening Visit, the ophthalmologic examination does not need to be repeated during the Screening Period.

In addition, at the Screening Visit, the following history will be obtained for all subjects:

- history of steroid use
- history or presence of diabetes
- any prior ophthalmologic or optometric examinations
- history of trauma to the eye
- any family history of glaucoma, congenital cataracts, or cataracts arising later in life
- use of corrective lenses (contact lenses or eyeglasses)
- history of prolonged exposure to sunlight or ultraviolet light and use of sunglasses
- history of exposure to secondhand smoke

Additional ophthalmologic examinations may be conducted at the discretion of the investigator. The Vertex medical monitor or designee should be notified of any additional ophthalmologic examinations.

11.5.7 Contraception and Pregnancy

11.5.7.1 Contraception

The effects of LUM and IVA combination therapy on conception, pregnancy, and lactation in humans are not known. Neither LUM nor IVA showed any genotoxic potential in a standard battery of in vitro (Ames, Chinese hamster ovary cell chromosomal aberration) and in vivo (mouse micronucleus) studies. LUM and IVA were each found to be non-teratogenic in reproductive toxicology studies in rats and rabbits (see the LUM/IVA Investigator's Brochure[29]). However, a metabolite of LUM, M28-lumacaftor, when given to pregnant rats at very high levels far beyond levels observed in humans (>100-fold), produced fetal malformations. The significance of this finding in humans is unclear, but is highly unlikely to be of any clinical significance. Subjects should follow the contraception requirements outlined in this protocol. The effects of LUM in combination with IVA on the pharmacokinetics of hormonal contraceptives are not known; however, since LUM is an inducer of CYP3A, it may reduce the effectiveness of hormonal contraceptives. Hormonal contraceptives should not be relied upon as an effective method of contraception.

Participation in this LUM/IVA study requires a commitment from the subject and his/her partner to use at least 1 effective method of birth control (as a couple). Acceptable methods

of contraception for subjects and their partners are listed below. Methods of contraception should be in successful use from at least 14 days before the first dose of study drug (unless otherwise noted) until 90 days after the last dose of study drug.

Contraception for the couple is waived for the following:

- True abstinence for the subject, when this is consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
- If the male is infertile (e.g., bilateral orchiectomy). Infertility may be documented through examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound before the first dose of the study drug.
- If the female is of non-childbearing potential, per the following:
    - Postmenopausal: spontaneous amenorrhea for at least 12 consecutive months and a serum FSH level ≥40 mIU/mL at the Screening Visit
    - Documented hysterectomy or a bilateral oophorectomy/salpingo-oophorectomy
    - Note: All other female subjects who have had their first menstrual period from the time of screening, or at any point through the Safety Follow-up Visit (including subjects with tubal ligations), will be considered to be of childbearing potential.

Acceptable Contraceptive Methods:

Acceptable contraceptive methods for **male subjects** or **male partners** of female subjects include the following:

- Vasectomy at least 6 months previously, with a negative post-vasectomy semen analysis for sperm
- Condom with spermicide (either as a single product if commercially available and/or allowed according to local regulations; otherwise, condom and spermicide as separate products). Local regulations may require use of an additional acceptable method of contraception.

Acceptable contraceptive methods for **female subjects** include the following:

- Bilateral tubal ligation performed at least 6 months previously
- Continuous use of an intrauterine device (non-hormone-releasing) for at least 90 days
- Barrier contraception (such as diaphragm, cervical cap, or female condom) with spermicide. Local regulations may require use of an additional acceptable method of contraception.
- Note: Hormonal contraceptives, including oral, injectable, transdermal, and implantable, will not be considered as an effective method; however, female subjects are not required to discontinue hormonal contraceptives.

Acceptable contraceptive methods for **female partners** of male subjects:

- Bilateral tubal ligation performed at least 6 months previously

- Continuous use of an intrauterine device for at least 90 days
- Barrier contraception (such as diaphragm, cervical cap, or female condom) with spermicide. Local regulations may require use of an additional acceptable method of contraception.
- Hormonal contraceptives, if successfully used for at least 60 days

Additional notes:

- Female condom cannot be used with male condom (as a double method of contraception) due to risk of tearing.
- Male and female subjects who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active with a partner of the opposite sex.
- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.
- Male subjects must not donate sperm after the first dose of study drug, throughout the study, and for 90 days after the last dose of study drug.
- Female subjects and female partners of male subjects should not plan to become pregnant during the study through 90 days after the last dose of study drug.
- Female subjects should not nurse a child from the start of study drug dosing through 90 days after the last dose of study drug.

Unique situations that may not fall within the above specifications may be discussed with the Vertex medical monitor or authorized designee on an individual basis.

11.5.7.2 Pregnancy

Subjects will be counseled to inform the investigator of any pregnancy that occurs during study treatment and for 90 days after the last dose of study drug.

If a subject or the female partner of a male subject becomes pregnant while participating in the study, study drug will be permanently discontinued immediately. The investigator will notify the medical monitor and Vertex Global Patient Safety within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form.

If the subject is confirmed to be on active drug, the subject or partner will be followed until the end of the pregnancy and the infant will be followed for 1 year after the birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

12 STATISTICAL AND ANALYTICAL PLANS

This section presents a summary of the planned analyses for this protocol. Statistical analysis details will be provided in the statistical analysis plan (SAP), which will be finalized before the clinical data lock for the study.

12.1 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 12-1 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, it is expected that additional data, independent of this study, will emerge while this study is underway and will allow more precise estimation of the true treatment effect. The final sample size will be based on these data, and the protocol may be amended as appropriate.

Table 12-1 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

12.2 Analysis Sets

The Full Analysis Set (FAS) is defined as all randomized subjects who have received at least 1 dose of study drug. The FAS will be used for all efficacy analyses, with subjects analyzed according to their randomized treatment group.

The Safety Set is defined as 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.

12.3 Statistical Analysis

This section presents a summary of the planned statistical analyses of efficacy and safety for this study. The Vertex Biometrics department or a designated CRO will analyze the data derived from this study.

12.3.1 General Considerations

All individual subject data for the FAS will be presented in data listings.

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

Categorical data will be summarized using counts and percentages.

Baseline for a variable will, unless specifically stated otherwise, be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the initial administration of study drug. For actigraphy variables, baseline will be the data collected for 1 week during the Screening Period.

Change from baseline will be calculated as post-baseline value minus baseline value.

12.3.2 Background Characteristics

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, study drug exposure and compliance, and other background characteristics will be summarized. Additionally, all subject data will be presented in data listings. All summaries will be based on the FAS unless otherwise specified in the SAP for the study. No statistical hypothesis testing will be performed on background characteristics.

12.3.2.1 Subject Disposition

Number and percentage of subjects in the following disposition categories will be summarized by treatment group:

- Randomized
- Dosed (Safety Set)
- Randomized and dosed (FAS)
- Completed Treatment Period
- Prematurely discontinued study drug before completing the assigned duration of dosing and the reasons for discontinuation
- Completed Safety Follow-up Visit
- Prematurely withdrawn from the study (did not complete Safety Follow-up Visit) and the reasons for withdrawal

12.3.2.2 Demographics and Baseline Characteristics

Demographic, background (e.g., medical history), and baseline characteristics will be summarized by treatment group. The following demographics and baseline characteristics will be summarized by treatment group for the FAS: sex, race, age, weight, height, BMI, baseline ppFEV$_1$, and site.

No statistical tests will be carried out to evaluate any baseline imbalance between treatment groups.

12.3.2.3 Prior and Concomitant Medications

Medications used in this study will be coded using the World Health Organization Drug Dictionary Enhanced and categorized as follows:

- **Prior medication:** any medication that 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 included in 1, 2, or all 3 of these categories. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether the medication was taken before initial dosing, concomitantly, or after 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 by treatment group based on the FAS. Post-treatment medications will be listed for each subject.

12.3.2.4 Study Drug Exposure and Compliance

Exposure to study drug (i.e., duration of treatment in days) will be defined as the last day minus the first day of study drug plus 1. Exposure will be summarized by treatment group for the Safety Set.

Dosing compliance will be calculated as the actual number of dosing occasions at which study drug was administered, as a percentage of the planned number of dosing occasions while the subject was on study drug (i.e., before study drug discontinuation or completion). Dosing compliance will be summarized for the FAS.

Duration of treatment and dosing compliance will be summarized by means of descriptive summary statistics.

12.3.2.5 Important Protocol Deviations

Important protocol deviations (IPDs) are defined as protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Protocol deviations will be reviewed before database lock in a blinded manner to establish rules for identifying the IPDs. The IPDs identified through this process will be presented in a data listing.

12.3.3 Efficacy Analysis

12.3.3.1 Analysis of Primary Variables

The primary efficacy endpoint is the percentage change from baseline in VO_{2max} during CPET at Week 24. The null hypothesis to be tested is that the mean percentage change from study baseline in VO_{2max} at Week 24 is the same for the LUM/IVA and placebo groups.

The primary analysis will use a restricted maximum likelihood (REML)-based mixed effect model for repeated measures (MMRM). The model will include the percentage change from

baseline in VO_{2max} as the dependent variable; treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect with adjustment for sex (male versus female), age group at baseline (<18 versus ≥18 years old), and $ppFEV_1$ at Screening (<70% versus ≥70%). In the model, visit will be treated as a class variable, and an unstructured covariance matrix will be assumed to model the within-subject variability, which imposes no assumptions on the correlational structure. Denominator degrees of freedom for the *F*-test for fixed effects will be estimated using the Kenward-Roger approximation. No imputation of missing data will be performed.

The primary result obtained from the model will be the estimated treatment effect at Week 24 based on a contrast test. The estimated mean treatment effect at Week 24, a 95% confidence interval, and a 2-sided *P* value will be provided. Furthermore, the treatment effect at each post-baseline visit, obtained from the model, also will be provided.

If there is a convergence problem due to the use of an unstructured covariance matrix, the unstructured covariance matrix will be replaced by compound symmetry in the primary analysis.

[redacted]

12.3.3.2 Analysis of Secondary Efficacy Variables

Key Secondary Efficacy Endpoint:

The key secondary efficacy endpoint is the change from baseline in exercise duration during CPET at Week 24. The same analysis method as for the primary efficacy endpoint will be used, with change from baseline in exercise duration as the dependent variable. To control for multiplicity, the test for change in exercise duration will only be considered statistically significant if the 2-sided *P* value is 0.05 or less and the test for the primary endpoint also is statistically significant.

Other Secondary Efficacy Endpoints:

All other secondary efficacy endpoints will be analyzed in a similar fashion. No adjustment for multiplicity will be made for these endpoints. The other secondary endpoints are listed in Section 7.2.

12.3.3.3 Correlation Analyses

The correlations between changes in exercise tolerance assessments and changes in selected efficacy outcome measures, including $ppFEV_1$ and BMI, will be calculated for each treatment group.

[redacted]

[redacted]

12.3.4 Safety Analysis

The overall safety profile of study treatments will be assessed in terms of the following safety endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values
- Vital signs
- Ophthalmologic examinations (for subjects under 18 years of age only)

Safety analysis will be based on the set of data associated with the period from the signing of informed consent through the Safety Follow-up Visit. Safety analyses will be based on the Safety Set. The summaries will be by treatment group, which will be defined according to the treatment actually received.

For safety variables, the scheduled Day 1, predose measurement will be used as the baseline value, when available; otherwise, the baseline value will be defined as the value at the Screening Visit.

All safety data will be listed by subject in data listings.

12.3.4.1 Adverse Events

AEs will be coded according to MedDRA. The number and percentage of subjects experiencing an AE will be summarized by the MedDRA system organ class and preferred term, as well as by treatment group. AEs will be classified as pretreatment or treatment-emergent.

Pretreatment AEs are defined as AEs that were reported or worsened after signing the ICF up to the start of study drug dosing.

Treatment-emergent AEs are defined as AEs that were reported or worsened on or after the start of study drug dosing through the 28-day Safety Follow-up Visit.

For an AE with a missing or partial start date, if there is no clear evidence that the AE started before or after study treatment, then the AE will be classified as a TEAE.

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

- All TEAEs
- TEAEs by relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation

- Serious TEAEs
- TEAEs leading to death
- Frequently reported TEAEs

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).

The following rules will apply to the summarization of AEs: (1) a subject with multiple occurrences of the same AE or a continuing AE will only be counted once; (2) only the maximum severity level will be presented in the severity summary; and (3) only the worst relationship level will be presented in the relationship summary.

All AEs through the Safety Follow-up Visit will be listed by subject in a data listing, including pretreatment AEs. AEs leading to death, dose interruption, and permanent discontinuation, as well as SAEs, will be listed separately.

12.3.4.2 Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using SI units. Hematology and clinical chemistry results will be summarized by treatment group at each scheduled time point. In addition, mean values at each visit will be plotted by treatment group for each of the liver function parameters.

A listing of abnormal individual subject hematology and clinical chemistry values from scheduled and unscheduled time points will be provided. Grade 3 toxicity laboratory values will be listed by subject in a data listing. Coagulation and urinalysis results will be listed only; these results will not be summarized. Clinically significant abnormal laboratory findings will be reported as AEs.

12.3.4.3 Electrocardiogram

ECG findings will be listed. Clinically significant abnormal findings will be reported as AEs.

12.3.4.4 Vital Signs

The following vital signs will be summarized by treatment group at each scheduled time point: systolic and diastolic blood pressure (mmHg), body temperature, pulse rate (beats per minute), and respiratory rate (breaths per minute). Clinically significant abnormal findings in vital signs will be reported as AEs.

The number and percentage of subjects who meet the abnormal criteria for the vital signs evaluation during the Treatment Period will be tabulated by treatment group: HR ≤50 bpm and a decrease from baseline ≥20 bpm, HR ≥120 bpm and an increase from baseline ≥20 bpm, systolic blood pressure ≤95 mm Hg and a decrease from baseline ≥20 mm Hg, systolic blood pressure ≥160 mm Hg and an increase from baseline ≥20 mm Hg, diastolic blood pressure ≤45 mm Hg and a decrease from baseline ≥10 mm Hg, diastolic blood pressure ≥110 mm Hg and an increase from baseline ≥10 mm Hg, weight ≥5% increase from baseline, and weight ≥5% decrease from baseline.

12.3.4.5 Physical Examination

PE results will be listed by subject in data listings only. Clinically relevant results identified after screening will be reported as AEs.

12.3.4.6 Other Safety Analysis

Ophthalmologic examination findings will be listed.

Spirometry data will be summarized descriptively as safety-supporting data. The following summaries will be provided at each visit based on the Safety Set:

- Numbers and percentages of subjects with decrease of ≥5 percentage points and with decrease of ≥10 percentage points in absolute change from baseline in $ppFEV_1$ at each visit.
- Numbers and percentages of subjects with ≥5% decrease and with ≥10% decrease in relative change from baseline in $ppFEV_1$ at each visit.
- Numbers and percentages of subjects with decrease of ≥0.05 L and with decrease of ≥0.10 L in absolute change from baseline in FEV_1 at each visit.
- Numbers and percentages of subjects with ≥5% decrease and with ≥10% decrease in relative change from baseline in FEV_1 at each visit.

Subjects with decrease of ≥5 percentage points in absolute change from baseline in $ppFEV_1$ or absolute change from baseline in FEV_1 at any visit will be listed. The listing will include raw values and absolute/relative changes from baseline in FEV_1 and $ppFEV_1$ at all visits.

12.3.5 Interim and IDMC Analyses

No interim analysis is planned.

No independent data monitoring committee (IDMC) will be used for this study.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

13.1 Adverse Event and Serious Adverse Event Documentation, Severity Grading, and Reporting

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or worsening of a pre-existing condition (e.g., increase in its severity or frequency) after the ICF is signed.

An AE is considered serious if it meets the definition in Section 13.1.2.1.

13.1.1.2 Clinically Significant Assessments

Study assessments including laboratory tests, PEs, and vital signs will be assessed and those deemed to have clinically significant worsening from baseline will be documented as an AE. When possible, a clinical diagnosis for the study assessment will be provided, rather than the abnormal test result alone (e.g., urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself will be listed as the AE (e.g., bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the subject has 1 or more of the following:

- Concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention
- A change in the dose of study drug or discontinuation from the study

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant will be made by the investigator.

A laboratory value that is Grade 4 will not automatically be an SAE. A Grade 4 laboratory value will be an SAE if the subject's clinical status indicates a life-threatening AE.

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time ICF is signed until the following time points:

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, the earliest of
    - 4 weeks after the last dose of study drug, or
    - the ETT Visit, if that visit is 3 weeks after the last dose of study drug or later (see Section 8.1.4).

All subjects will be queried, using nonleading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms will be identified as 1 overall event or diagnosis. All AEs for enrolled subjects will be recorded in the CRF and source document. AEs for subjects who are screened, but not subsequently enrolled in the study, will be recorded only in the subject's source documents. The following data will be documented for each AE:

- Description of the event
- Classification of "serious" or "nonserious"
- Date of first occurrence and date of resolution (if applicable)

- Severity
- Causal relationship to study drug(s)
- Action taken
- Outcome
- Concomitant medication or other treatment given

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (accessed January 2016). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." In considering the severity of an AE in a pediatric subject, the investigator will consider that reference ranges for pediatric clinical laboratory parameters may differ from those given in the CTCAE. The severity of an AE that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

Classification	Definition
Mild (Grade 1)	Mild level of discomfort and does not interfere with regular activities
Moderate (Grade 2)	Moderate level of discomfort and significantly interferes with regular activities
Severe (Grade 3)	Significant level of discomfort and prevents regular activities
Life-threatening (Grade 4)	Any adverse drug event that places the subject, in the view of the investigator, at immediate risk of death

13.1.1.5 Adverse Event Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug(s). Causality will be classified using the categories presented in Table 13-2.

Table 13-2 Classifications for AE Causality

Classification	Definition
Related	There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event reappeared on re-exposure to the investigational study drug.
Possibly related	There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
Unlikely related	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
Not related	The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the study subject's medical records).

13.1.1.6 Study Drug Action Taken

The investigator will classify the study drug action taken with regard to the AE. The action taken will be classified according to the categories shown in Table 13-3.

Table 13-3 Classifications for Study Drug Action Taken With Regard to an AE

Classification	Definition
Dose not changed	Study drug dose not changed in response to an AE
Dose reduced	Study drug dose reduced in response to an AE
Drug interrupted	Study drug administration interrupted in response to an AE
Drug withdrawn	Study drug administration permanently discontinued in response to an AE
Not applicable	Action taken regarding study drug administration does not apply. "Not applicable" will be used in circumstances such as when the investigational treatment had been completed before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible.

13.1.1.7 Adverse Event Outcome

An AE will be followed until the investigator has determined and provided the final outcome. The outcome will be classified according to the categories shown in Table 13-4.

Table 13-4 Classifications for Outcome of an AE

Classification	Definition
Recovered/Resolved	Resolution of an AE with no residual signs or symptoms
Recovered/Resolved With Sequelae	Resolution of an AE with residual signs or symptoms
Not Recovered/Not Resolved (Continuing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing
Fatal	Outcome of an AE is death. "Fatal" will be used when death is at least possibly related to the AE.
Unknown	Outcome of an AE is not known (e.g., a subject lost to follow-up)

13.1.1.8 Treatment Given

The investigator ensures adequate medical care is provided to subjects for any AEs, including clinically significant laboratory values related to study drug. In addition, the investigator will describe whether any treatment was given for the AE. "Yes" is used if any treatment was given in response to an AE, and may include treatments such as other medications, hospitalization, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

An SAE is any AE that meets any of the following outcomes:

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation in the study and is suspected of being a delayed toxicity due to administration of the study drug)
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Congenital anomaly or birth defect
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home)

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the subject signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure will not be considered to indicate an SAE, unless an AE caused the hospitalization or procedure to be rescheduled sooner or to be prolonged relative to what was planned. In addition, hospitalizations clearly

not associated with an AE (e.g., social hospitalization for purposes of respite care) will not be considered to indicate an SAE.

Clarification will be made between the terms "serious" and "severe" because they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event, as in mild, moderate, or severe myocardial infarction. The event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on subject/event outcome or action described above, and is usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining expedited regulatory reporting obligations.

13.1.2.2 Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through the Safety Follow-up Visit, regardless of causality, will be reported by the investigator to Vertex GPS. In addition, all SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours**.

SAEs will be recorded on the Vertex Organized Safety Information Collection Form (hereafter referred to as the "SAE Form") using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for relationship to the investigational study drug(s) and possible etiologies. On the SAE Form, relationship to study drug(s) will be assessed only as related (includes possibly related) or not related (includes unlikely related), and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report to Vertex the outcome of the event using the SAE Form.

13.1.2.3 Reporting Serious Adverse Events

The investigator is responsible for notifying the sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. The SAE Form will be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (Preferred Choice)

Fax: [redacted]

Contact Telephone: [redacted]

13.1.2.4 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as

applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to central IECs.

It is the responsibility of the investigator or designee to promptly notify the local IRB/local IEC of all unexpected serious adverse drug reactions involving risk to human subjects.

13.2 Administrative Requirements

13.2.1 Ethical Considerations

The study will be conducted in accordance with the current ICH GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local applicable laws and regulations. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

13.2.2 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject or legal representative or guardian (if applicable), and assent will be obtained from the subject (if applicable), before study participation. The method of obtaining and documenting the informed consent and assent (if applicable) and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

13.2.3 Investigator Compliance

No modifications to the protocol will be made without the approval of both the investigator and Vertex. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (i.e., efficacy assessments) will require IRB/IEC notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. Vertex will submit all protocol modifications to the required regulatory authorities.

When circumstances require an immediate departure from procedures set forth in the protocol, the investigator will contact Vertex to discuss the planned course of action. If possible, contact will be made before the implementation of any changes. Any departures from the protocol will be fully documented in the source documentation and in a protocol deviation log.

13.2.4 Access to Records

The investigator will make the office and/or hospital records of subjects enrolled in this study available for inspection by Vertex or its representative at the time of each monitoring visit and for audits. The records will also be available for direct inspection, verification, and copying, as required by applicable laws and regulations, by officials of the regulatory health authorities (FDA and others). The investigator will comply with applicable privacy and

security laws for use and disclosure of information related to the research set forth in this protocol.

13.2.5 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all CRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers and access to subject names linked to such numbers shall be limited to the site and the study physician and shall not be disclosed to Vertex. As required by applicable laws and regulations in the countries in which the study is being conducted, the investigator will allow Vertex and/or its representatives access to all pertinent medical records to allow for the verification of data gathered in the CRFs/SAE forms and the review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/IEC, may also request access to all study records, including source documentation, for inspection.

For sites participating in the study in the US, and in accordance with the Health Insurance Portability and Accountability Act and associated regulations ("HIPAA") an executed HIPAA authorization shall be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization shall comply with all HIPAA requirements including authorization allowing the site access to and use of the subject's personally identifiable health information, authorization for the site to disclose such information to Vertex, the FDA, and other parties requiring access under the protocol, and statements as to the purpose for which such information may be used and for how long.

13.2.6 Record Retention

The investigator will maintain all study records according to ICH GCP guidelines and/or applicable local regulatory requirement(s), whichever is longest, as described in the Clinical Trial Agreement. If the investigator withdraws from the responsibility of keeping the study records, custody will be transferred to a person willing to accept the responsibility and Vertex will be notified.

13.2.7 Study Termination

At any time, Vertex may terminate this study in its entirety or may terminate this study at any particular site. In addition, for reasonable cause, either the investigators or their IRBs/IECs may terminate the study at their center.

Conditions that may lead to reasonable cause and warrant termination include, but are not limited to:

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects

- Decision to modify drug development plan
- Decision by the FDA or other regulatory authority

Written notification that includes the reason for the clinical study termination is required.

13.3 Data Quality Assurance

Vertex or its designated representative will conduct a study site visit to verify the qualifications of each investigator, inspect clinical study site facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure, validated, web-based electronic data capture (EDC) application. Vertex will have read-only access to site-entered clinical data in the EDC application.

Instances of missing, discrepant, or uninterpretable data will be queried with the investigator for resolution. Any changes to study data will be made to the CRF and documented in an audit trail, which will be maintained within the clinical database.

13.4 Monitoring

Monitoring and auditing procedures developed or approved by Vertex will be followed to comply with GCP guidelines. On-site checking of the CRFs/SAE Forms for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by Vertex or its designee. Monitoring will be done by personal visits from a representative of Vertex, or designee (study site monitor), who will review the CRFs/SAE Forms and source documents. The study site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

13.5 Electronic Data Capture

Vertex will provide the study sites with secure access to and training on the EDC application sufficient to permit study site personnel to enter or correct information in the CRFs on the subjects for which they are responsible.

A CRF will be completed for each enrolled study subject. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data will indicate the subject's participation in the study and will document the dates and details of study procedures, AEs, other observations, and subject status.

The investigator, or designated representative, will complete the CRF as soon as possible after information is collected.

The audit trail entry will show the user's identification information and the date and time of any correction. The investigator will provide formal approval of all the information in the

CRFs, including any changes made to the CRFs, to endorse the final submitted data for the subjects for whom the investigator is responsible.

Vertex will retain the CRF data and corresponding audit trails. A copy of the final archival CRF in the form of a CD or other electronic media will be placed in the investigator's study file.

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX15-809-112	Version #: 1.0	Version Date: 15 January 2016
Study Title: 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 Clinical Study Protocol has been reviewed and approved by the sponsor.

Printed Name	Title
Signature	Date

15.2 Investigator Signature Page

Protocol #: VX15-809-112	Version #: 1.0	Version Date: 15 January 2016
Study Title: 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		

I have read Protocol VX15-809-112, Version 1.0, and agree to conduct the study according to its terms. I understand that all information concerning lumacaftor/ivacaftor and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) are confidential.

Printed Name

Signature Date