1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Efficacy of Lumacaftor/Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis Who Have an *A455E-CFTR* Mutation

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2 PROTOCOL SYNOPSIS

Title

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Efficacy of Lumacaftor/Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis Who Have an *A455E-CFTR* Mutation

Brief Title

Lumacaftor/Ivacaftor Combination Therapy in Subjects With CF Who Have an *A455E-CFTR* Mutation

Clinical Phase and Clinical Study Type

Phase 2, double-blind, placebo-controlled, crossover

Objectives

Primary Objective

To evaluate the efficacy of lumacaftor/ivacaftor combination therapy (LUM/IVA) in subjects with cystic fibrosis (CF) 12 years of age and older who have at least one *A455E* mutation.

[redacted]

Endpoints

Primary Endpoint

Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) through 8 weeks of treatment.

[redacted]

Number of Subjects

Approximately 20 subjects.

Study Population

Male and female subjects 12 years of age and older with CF, with an *A455E* mutation on at least 1 *CFTR* allele, and with forced expiratory volume in 1 second (FEV_1) ≥30% of predicted and ≤90% of predicted.

Investigational Drug

Active substance: LUM/IVA fixed-dose combination

Activity: CFTR corrector and potentiator (chloride ion secretion)

Strength and route of administration: 200-mg lumacaftor/125-mg ivacaftor (200/125 mg) film-coated tablets for oral administration

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

Study Duration

The total study duration for each subject will be approximately 32 weeks, including the Screening and Follow-up periods.

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter, crossover study. The crossover design includes two 8-week treatment periods separated by an 8-week (± 7 days) washout period. Subjects will be randomized (1:1) to 1 of 2 treatment sequences: LUM/IVA followed by placebo or placebo followed by LUM/IVA.

Assessments

Efficacy: Spirometry (excluding assessments on Day 2 and the day after the Week 16 Visit [if applicable]); [redacted]

Safety: Adverse events (AEs), clinical laboratory assessments (liver function tests), ophthalmologic examinations (for subjects less than 18 years of age), vital signs, and spirometry (on Day 2 and the day after the Week 16 Visit only, for subjects with FEV_1 <40% of predicted)

[redacted]

Statistical Analyses

Sample Size: No formal sample size calculation is to be conducted for this study. The planned sample size of approximately 20 subjects is based on the number of subjects expected to be available for participation.

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 efficacy analyses. The Safety Set is defined as all subjects who received at least 1 dose of study drug. The Safety Set will be used for safety analyses.

Efficacy Analysis: The analysis of the absolute change from baseline in $ppFEV_1$ through 8 weeks of study drug treatment will be based on a mixed-effects model for repeated measures utilizing the FAS. The estimated mean treatment difference overall, a 95% CI, and a 2-sided *P* value will be provided. The estimated mean treatment difference at each visit along with the corresponding 95% CI and *P* value will also be presented. Raw values and changes from baseline will be summarized by treatment group using descriptive statistics. Paired *t*-tests for the difference between treatments for each subject, as well as Wilcoxon signed-rank tests, may be provided.

Safety Analysis: The incidence of treatment-emergent AEs will be summarized in contingency tables (n, percentage) by treatment. For other safety parameters (e.g., vital signs), the raw values and changes from baseline will be summarized by treatment. Additionally, all safety data will be presented in subject data listings.

3 SCHEDULE OF ASSESSMENTS

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

Table 3-1 Study VX15-809-111: Screening Period Assessments

Assessment	Screening Period (Day -28 through Day -1)
Informed consent and assent (when applicable)	X
Review inclusion/exclusion criteria	X
Demographics	X
Medical history	X
CFTR genotyping[a]	If deemed necessary by investigator
Ophthalmological history	X
Prior and concomitant medications	X
Ophthalmologic examination[b]	X
Complete physical examination	X
Weight, height[c]	X
Vital signs and pulse oximetry[d]	X
Spirometry[e]	X
[redacted]	
FSH[f]	X
Serum pregnancy test (females of childbearing potential)[g]	X
Hematology	X
Serum chemistry	X
AEs and SAEs	Continuous from signing of the ICF and Assent Form (where applicable) through the Follow-up Visit

[a] It is expected that most subjects will have documentation of *CFTR* genotype in their medical records. If documentation of *CFTR* genotype is not available, or if confirmation of *CFTR* genotype is deemed necessary by the investigator, *CFTR* genotyping will be performed during the Screening Period.

[b] Ophthalmologic examination is required for subjects who are less than 18 years of age at the Screening Visit. If there is documentation of an ophthalmologic examination that met protocol criteria and was conducted within 3 months before the Screening Visit, the subject is not required to have a repeat ophthalmologic examination during Screening.

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

[d] Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) and pulse oximetry will be collected after the subject has been at rest (seated or supine) for at least 5 minutes. Blood pressure will be measured by sphygmomanometer.

[e] At Screening, spirometry may be performed pre- or post-bronchodilator.

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

[g] See Section 11.6.7.1 for definition of childbearing potential.

Table 3-2 Study VX15-809-111: Treatment Period Assessments

Event/Assessment	Treatment Period 1				Washout Period (No Visit)	Treatment Period 2				Early Termination of Treatment (ETT)
	Day 1	Day 2[a]	Week 4 (± 4 days)	Week 8 (± 7 days)	8 weeks (± 7 days)	Week 16 (± 4 days)	Day after Week 16 Visit[a]	Week 20 (± 4 days)	Week 24 (± 7 days)	
Review inclusion/ exclusion criteria[b]	X									
Randomization	X									
[redacted]										
Vital signs[g]	X	X	X	X		X	X	X	X	X
Pulse oximetry		X					X			
Spirometry[h]	X	X	X	X		X	X	X	X	X
[redacted]										
Urine pregnancy test[i]	X		X	X		X		X	X	X

[a] These visits will be conducted for subjects whose FEV_1 at Screening is <40% of predicted.

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

[redacted]

[g] Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be collected after the subject has been at rest (seated or supine) for at least 5 minutes. Blood pressure will be measured by sphygmomanometer.

[h] Spirometry will be performed pre-bronchodilator and must be performed before study drug dosing.

[i] Pregnancy tests will be performed for all female subjects of childbearing potential. The urine β-hCG tests on Day 1 and Week 16 must be negative before the study drug is administered.

Table 3-2 Study VX15-809-111: Treatment Period Assessments

Event/Assessment	Treatment Period 1				Washout Period (No Visit)	Treatment Period 2				Early Termination of Treatment (ETT)
	Day 1	Day 2[a]	Week 4 (± 4 days)	Week 8 (± 7 days)	8 weeks (± 7 days)	Week 16 (± 4 days)	Day after Week 16 Visit[a]	Week 20 (± 4 days)	Week 24 (± 7 days)	
Liver function tests (LFTs)[j]	X			X		X			X	X
Ophthalmologic examination[k]									X[l]	X[l]
[redacted]										
Meal(s) or snack(s) at site[n]	X	X	X	X		X	X	X	X	
Study drug dosing	**Day 1 through Week 8** (Last dose of study drug will be administered the day before the Week 8 Visit)				**No study drug**	**Week 16 through Week 24** (Last dose of study drug will be administered the day before the Week 24 Visit)				
Observation 4 h after dosing[o]	X					X				
Concomitant medications	X	X	X	X		X	X	X	X	X
Concomitant treatments and procedures	X	X	X	X		X	X	X	X	X
AEs and SAEs	**Continuous from signing of the ICF and Assent Form (where applicable) through the Follow-up Visit**									

j ALT, AST, GGT, alkaline phosphatase, and bilirubin.
k For subjects who were less than 18 years of age at the Screening Visit.
l Ophthalmologic examination will be performed at the Week 24 Visit, the Early Termination of Treatment Visit, **or** the Follow-up Visit. This examination is not required if the subject received the study drug for a total of less than 4 weeks.
[redacted]
n Fat-containing food such as a standard "CF" high-fat, high-calorie meal or snack will be provided to subjects at the site after all predose assessments have occurred.
o Observation 4 h after dosing will be performed for subjects whose FEV_1 at Screening is <40% of predicted.

Table 3-3 Study VX15-809-111: Follow-up Visit Assessments

Event/Assessment	Follow-up 4 weeks (± 7 days) after last dose of study drug
Vital signs[a]	X
[redacted]	
Spirometry[d]	X
[redacted]	
Serum pregnancy test[e]	X
LFTs[f]	X
Ophthalmologic examination[g,h]	X
[redacted]	
Concomitant medications	X
Concomitant treatments and procedures	X
AEs and SAEs	**Continuous from signing of the ICF and Assent Form (where applicable) through the Follow-up Visit**

[a] Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be collected after the subject has been at rest (seated or supine) for at least 5 minutes. Blood pressure will be measured by sphygmomanometer.

[redacted]

[redacted]

[d] Spirometry will be performed pre-bronchodilator.

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

[f] ALT, AST, GGT, alkaline phosphatase, and bilirubin.

[g] For subjects who were less than 18 years of age at the Screening Visit.

[h] Ophthalmologic examination will be performed at the Week 24 Visit, the Early Termination of Treatment Visit, **or** the Follow-up Visit. This examination is not required if the subject received study drug for a total of less than 4 weeks.

[redacted]

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5 INTRODUCTION

5.1 Cystic Fibrosis and Current Treatments

Cystic fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality and at present, there is no cure. CF affects an estimated 70,000 children and adults worldwide[1] and is the most common fatal genetic disease in persons of European descent.[2] Based on the size of the population, CF qualifies as an orphan disease.[3,4] 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.[5,6,7]

CF is caused by reduced quantity and/or function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein due to mutations in the *CFTR* gene. The CFTR protein is an epithelial chloride channel that aids in regulating salt and water absorption and secretion and pH balance in multiple organs, including the lungs, pancreas and other gastrointestinal organs, and sweat glands.[2] In people with CF, decreased CFTR chloride transport results in multisystem pathology. Although the disease affects multiple organs, progressive loss of lung function is the leading cause of mortality.[8]

More than 2000 mutations in the *CFTR* gene have been identified.[9] 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, and ivacaftor (IVA) is a CFTR potentiator. Lumacaftor/ivacaftor combination therapy (LUM/IVA) is approved in the US for the treatment of CF in patients 6 years of age and older who are homozygous for the *F508del* mutation, and in the EU, Canada, Australia, Switzerland, and Israel for the treatment of CF in patients 12 years of age and older who are homozygous for the *F508del* mutation, the most common mutation of the *CFTR* gene. Further information about LUM/IVA can be found in the Package Insert and Summary of Product Characteristics.[10,11]

5.2 Rationale for Study

The *A455E-CFTR* mutation is reported to occur in less than 0.1% of patients with CF worldwide,[12] but large regional differences in prevalence exist. In The Netherlands, it is the second most prevalent mutation, occurring in 3.6% of all patients with CF.[13] An especially high prevalence has been reported in the Southeast and Southwest regions of The Netherlands.[14] Although it was initially reported that the *A455E* mutation is associated with mild lung disease[15], current clinical experience in The Netherlands shows marked differences

in clinical disease severity, ranging from relatively mild to severe loss of lung function at young adulthood.

The *A455E* mutation results in a severe reduction of mature CFTR protein at the cell surface. In recent research, it was noted that when both *F508del-CFTR* and *264del-CFTR* were transfected into the same cells, the expression of mature F508del-CFTR protein was increased. Similarly, when both *A455E-CFTR* and *264del-CFTR* were transfected into the same cells, the expression of mature A455E-CFTR protein was increased. Furthermore, compounds known to be able to rescue F508del-CFTR were also able to rescue A455E-CFTR in vitro. This suggests that A455E-CFTR could be rescued by the same strategies as F508del-CFTR. These findings suggested that *A455E* might be a suitable candidate for LUM/IVA treatment.[16]

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the efficacy of LUM/IVA in subjects with CF 12 years of age and older who have at least one *A455E* mutation.

[redacted]

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) through 8 weeks of treatment.

[redacted]

8 STUDY DESIGN

8.1 Overview of Study Design

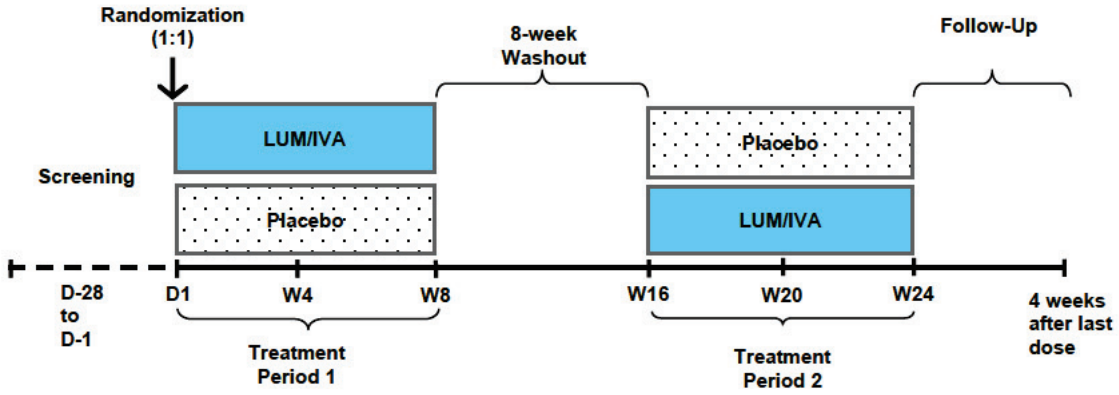
This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter, crossover study (Figure 8-1). The crossover design includes two 8-week treatment periods separated by an 8-week (± 7 days) washout period. There will be 7 to 9 study visits, not including the Screening Period. The total study duration for each subject will be approximately 32 weeks, including the Screening and Follow-up periods.

Subjects will be randomized 1:1 to receive 1 of 2 treatment sequences:

- Sequence 1: LUM/IVA in Treatment Period 1; washout; placebo in Treatment Period 2
- Sequence 2: placebo in Treatment Period 1; washout; LUM/IVA in Treatment Period 2

It is recommended that subjects maintain a stable CF medication regimen, as discussed in Section 9.3.1.

Figure 8-1 Study Design



8.1.1 Screening

The Screening Period will occur within 28 days before the first dose of study drug to confirm that the subjects meet the selection criteria for the study. The assessments to be conducted are shown in Table 3-1. The investigator (or an appropriate authorized designee) will obtain informed consent and assent, if applicable, from each subject.

It is expected that most subjects will have documentation of *CFTR* genotype in their medical records. If documentation of *CFTR* genotype is not available, or if confirmation of *CFTR* genotype is deemed necessary by the investigator, *CFTR* genotyping will be performed during the Screening Period.

Subjects who are less than 18 years of age at the Screening Visit will undergo an ophthalmologic examination during the Screening Period. If there is documentation of an ophthalmologic examination that met protocol criteria (Section 11.6.5) and was conducted within 3 months before the Screening Visit, the subject is not required to have a repeat ophthalmologic examination during the Screening Period.

8.1.1.1 Repetition of Screening Assessments

Repetition of individual screening assessment(s) that did not meet eligibility criteria is not permitted, with the following exceptions:

- If there is clear evidence of a laboratory error (e.g., hemolyzed sample) or equipment malfunction, collection of a repeat sample for the appropriate laboratory test or assessment may be permitted with the approval of the medical monitor.
- Exclusionary liver function test (LFT) levels may be retested within 14 days after the original screening date.
- If screening spirometry measurements fail to meet acceptability and repeatability criteria as specified by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines[18], repeat spirometry evaluation may be performed once.

If repeat values of the individual assessment(s) are within the eligibility criteria and completed within the screening window, then the subject is eligible for the study.

8.1.1.2 Rescreening

Subjects may be rescreened only with the approval of the medical monitor. If a subject is rescreened, all screening assessments will be repeated except for *CFTR* genotyping, follicle-stimulating hormone (FSH) level (if serum FSH level was ≥40 mIU/mL during prior screening), sweat chloride, rectal biopsy, and ophthalmologic examination (if performed within the last 3 months). A subject may be rescreened only once. If a subject is rescreened, the screening window will begin once the first rescreening assessment has been initiated.

8.1.1.3 Extension of the Screening Period Window

A subject may have the Screening Period window extended by 1 week for the following reasons:

- Repetition of the Screening Period assessments (Section 8.1.1.1)
- Additional time to schedule and conduct the ophthalmologic examination (Section 11.6.5)

8.1.2 Treatment Period 1

Study visits and assessments during Treatment Period 1 are listed in Table 3-2. Subjects will be outpatients during Treatment Period 1. All visits should occur within the windows specified. Subjects will be randomized to 1 of 2 sequences, as shown in Section 8.1.

The first dose of study drug will be administered on Day 1. Dosing details are given in Section 10.5. For subjects who are on a stable regimen of inhaled cycling antibiotics, the timing of the Day 1 Visit is described in Section 9.3.1.

The last dose of study drug in Treatment Period 1 will be administered the day before the Week 8 Visit.

Subjects who prematurely discontinue study drug treatment will be asked to come to the study site for an Early Termination of Treatment (ETT) Visit and a Follow-up Visit as described in Section 8.1.6.

8.1.3 Washout Period

Subjects will have a Washout Period lasting 8 weeks (± 7 days). No visits are scheduled during the Washout Period.

8.1.4 Treatment Period 2

Study visits and assessments during Treatment Period 2 are listed in Table 3-2. Subjects will be outpatients during Treatment Period 2. All visits should occur within the windows specified.

In order to participate in Treatment Period 2, subjects must not have an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before the Week 16 Visit (first dose of study drug in Treatment Period 2) and must not have had a non-CF-related illness within 2 weeks before

the Week 16 Visit. "Illness" is defined as an acute (serious or nonserious) condition (e.g., gastroenteritis). If a subject does not meet these criteria, then the continuation of the subject into Treatment Period 2 will be discussed with the medical monitor.

The first dose of study drug in Treatment Period 2 will be administered at the Week 16 Visit. Dosing details are given in Section 10.5. For subjects who are on a stable regimen of inhaled cycling antibiotics, the timing of the Week 16 Visit is described in Section 9.3.1.

The last dose of study drug in Treatment Period 2 will be administered the day before the Week 24 Visit.

Subjects who prematurely discontinue study drug treatment will be asked to come to the study site for an ETT Visit and a Follow-up Visit as described in Section 8.1.6.

8.1.5 Follow-up

Subjects will have a Follow-up Visit 4 weeks after the last study drug dose. Follow-up Visit assessments are listed in Table 3-3.

8.1.6 Early Termination of Treatment

Subjects who prematurely discontinue study drug treatment will be asked to come to the study site for an ETT Visit as soon as possible after stopping study drug and to complete the Follow-up Visit 4 weeks after the last dose of study drug. The assessments performed at the ETT Visit are listed in Table 3-2, and the assessments performed at the Follow-up Visit are listed in Table 3-3.

8.2 Rationale for Study Design and Study Drug Regimens

8.2.1 Study Design

A crossover design with a 1:1 randomization to the 2 treatment sequences will enable within-subject comparison of the effects of placebo and LUM/IVA. The design allows a comparison between placebo and LUM/IVA in this study with a limited population of potential subjects. The use of placebo is necessary in order to provide a robust assessment.

8.2.2 Study Drug Dose and Duration

8.2.2.1 Dose of LUM and IVA

The LUM 400 mg q12h/IVA 250 mg q12h dose regimen has been approved in the US, EU, Canada, Australia, Switzerland, and Israel for the treatment of CF in patients 12 years of age and older who are homozygous for the *F508del* mutation.[10,11]

8.2.2.2 Duration of Dosing

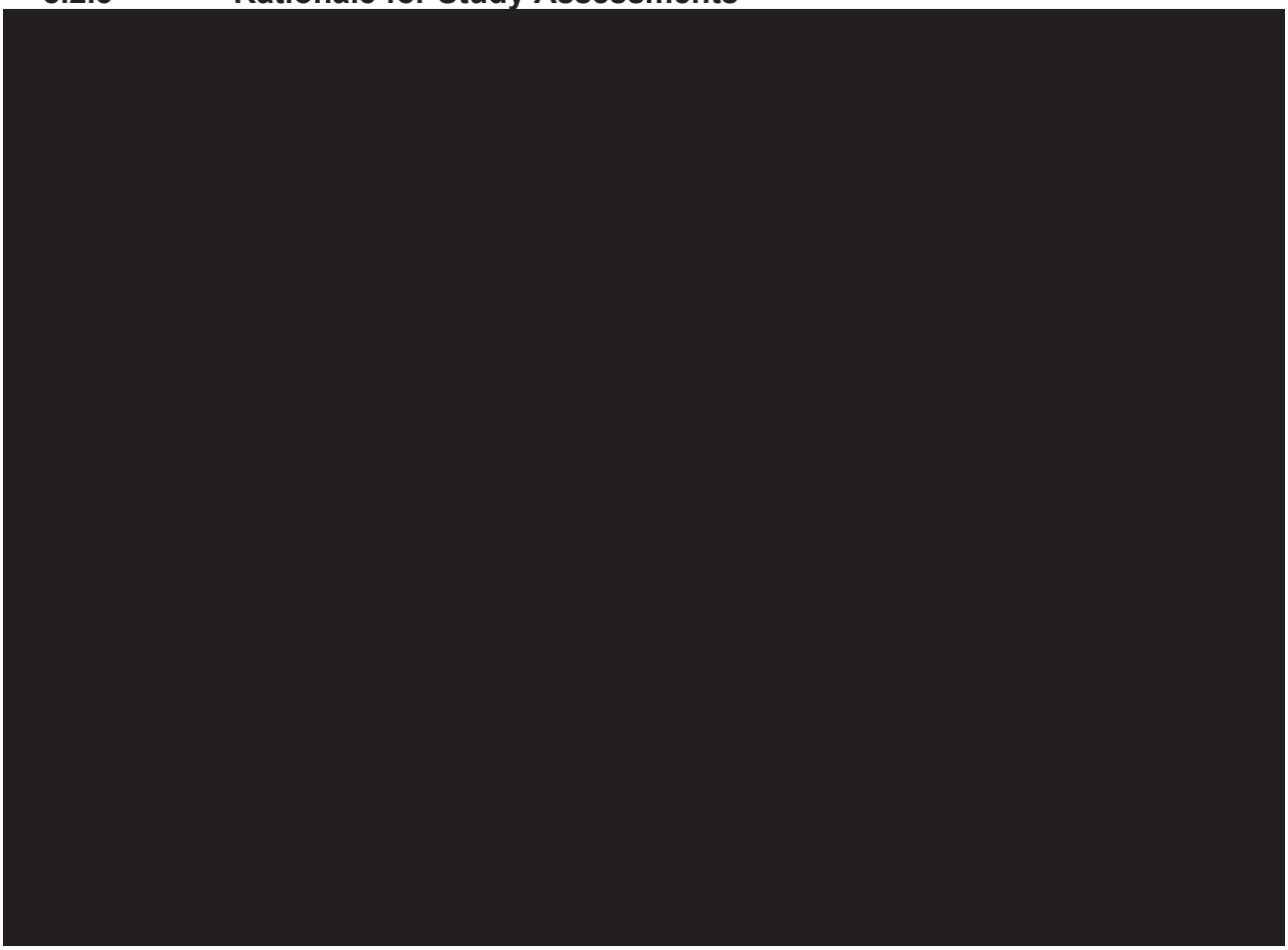
The 8-week duration of dosing in each Treatment Period was chosen based on results of the pivotal, placebo-controlled, Phase 3 studies VX12-809-103 and VX12-809-104, in which the effect of LUM/IVA therapy was assessed in patients with CF homozygous for *F508del*. These studies showed a clear improvement of $ppFEV_1$ after 8 weeks of treatment.[19,20]

8.2.2.3 Washout Period

An 8-week period was selected as the duration for the Washout Period. It is expected that some subjects will be on 28-day-on/28-day-off cycles of stable CF medication, as discussed in Section 9.3.1. An 8-week washout period is compatible with these cycles.

Washout periods are generally considered adequate if they encompass 5 half-lives of the administered compound. The apparent terminal half-life of LUM is 26 hours[10,11], and the apparent terminal half-life of IVA is 12 hours.[21] Thus, after an 8-week washout, levels of LUM and IVA are expected to be negligible. Based on data from previous studies of IVA and LUM/IVA, no residual effects of study drugs are expected by the end of the 8-week washout period.

8.2.3 Rationale for Study Assessments



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. Male or female with confirmed diagnosis of CF.[23] The subject must have **both** of the following:
    - One or more characteristic phenotypic features, such as chronic cough and sputum production, persistent chest radiograph abnormalities, **or** airway obstruction manifested by wheezing and air trapping; **or** a history of CF in a sibling; **or** a positive newborn screening test result;
    - An increased sweat chloride concentration by pilocarpine iontophoresis on two or more occasions; **or** identification of two CF mutations; **or** demonstration of abnormal nasal epithelial ion transport.
2. Age 12 years or older on the date of informed consent.
3. All subjects must have an *A455E* mutation on at least 1 *CFTR* allele.
4. Forced expiratory volume in one second (FEV_1) ≥30% of predicted and ≤90% of predicted at the Screening Visit, based on the Global Lung Function Initiative (GLI)-2012 multi-ethnic all-age reference equations.[24]
5. Stable CF disease as judged by the investigator.
6. Willing to remain on a stable medication regimen for CF from 4 weeks before Day 1 through the Follow-up Visit.
7. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
8. Subject (or subject's legally appointed and authorized representative) will sign and date an informed consent form (ICF), and where appropriate, assent form.

9.2 Exclusion Criteria

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

1. History of any comorbidity reviewed at the Screening Visit that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject. For example:
    - A history of cirrhosis with portal hypertension.
    - An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (the first dose of study drug).

2. A *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *R117H* mutation on at least one *CFTR* allele.
3. Ongoing or prior participation in an investigational drug study (including studies investigating LUM/IVA or IVA) within 30 days before the Screening Visit.
    - A washout period of 5 terminal half-lives of the previous investigational study drug or 30 days, whichever is longer, must elapse before the Screening Visit. The duration of the elapsed time may be longer if required by local regulations.
    - Subjects who participated in Vertex Study VX14-661-108 may not be enrolled.
    - Ongoing participation in a noninterventional study (including observational studies) is permitted.
4. Pregnant or breastfeeding.
5. Any of the following abnormal laboratory values at the Screening Visit:
    - 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
        - alkaline phosphatase ≥3 × ULN
    - ALT or AST >5 × ULN
    - Bilirubin >2 × ULN
    - Glomerular filtration rate ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation).[25]
6. History of cataract/lens opacity, or evidence of cataract/lens opacity determined to be clinically significant by the ophthalmologist or optometrist during the ophthalmologic examination at the Screening Visit (if applicable).
7. Use of strong inhibitors or strong inducers of CYP3A, including consumption of certain herbal medications (e.g., St. John's Wort) and certain fruit and fruit juices, within 14 days before Day 1 (the first dose of study drug).
8. Sexually active subjects of reproductive potential who are not willing to follow the contraception requirements outlined in Section 11.6.5.

9.3 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 Follow-up Visit, will be recorded in each subject's source documents and electronic case report form (eCRF). For subjects who are

screened but not enrolled, details of prior medications will only be documented in the subjects' source documents.

Information about bronchodilator use during the study will be collected and documented in the subject's source documents and eCRF.

9.3.1 Maintenance of Stable Medication Regimen for CF

It is recommended that subjects remain on stable CF medication regimens from 4 weeks before Day 1 through the Follow-up Visit. A stable medication regimen is defined as a medication regimen that the subject has been following for at least 4 weeks before Day 1.

Specific requirements apply to certain CF medications:

- Subjects who, at the time of study entry, are on a stable regimen of a single inhaled antibiotic that is continuously administered should remain on this antibiotic through the Follow-up Visit.
- Subjects who are on a stable regimen of a single inhaled cycling antibiotic (e.g., Tobramycin Inhalation Solution [TOBI®] regimen) at the time of study entry should remain on this antibiotic through the Follow-up Visit. Inhaled cycling antibiotics should be administered in 28-day-on/28-day-off cycles. Study visits on Day 1 and Week 8 during Treatment Period 1 and on Week 16 and Week 24 during Treatment Period 2 should be timed to occur at the end of an off-cycle and at least 14 days after the last dose of inhaled antibiotics in the previous on-cycle.
- Subjects who are on an alternating regimen of inhaled cycling antibiotics that comprise continuous administration of antibiotics (e.g., TOBI administration alternating with Cayston®) at the time of study entry should remain on these antibiotics according to their alternating regimens through the Follow-up Visit.

9.3.2 Prohibited Medications

Prohibited medications and certain foods are not allowed while subjects are receiving study drug (Table 9-1). A nonexhaustive list of prohibitions and cautions for food and medication will be provided in the Study Reference Manual.

Table 9-1 Study Restrictions

	Study Period	
Restricted Medication/Food	**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.

The use of moderate CYP3A inducers and inhibitors is not prohibited.

Use of CYP2B6 and CYP2C substrates is not prohibited. In vitro studies suggest that LUM has the potential 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/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 concomitantly with LUM/IVA during this study. Investigators should discuss any concerns regarding the use of these substrates with the medical monitor.

9.4 Removal of Subjects from Study Drug Treatment

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. Study drug treatment will be withdrawn for any female subject who has a confirmed pregnancy and for any male subject whose female partner has a confirmed pregnancy. A subject may be withdrawn from study drug treatment after a discussion between the investigator and the medical monitor for any of the following reasons:

1. The subject develops a medical condition that requires prolonged concomitant therapy with a prohibited medication or prolonged interruption of study drug.
2. The subject has an increase in transaminases for which withdrawal of study drug is recommended, as described in Section 11.6.3.
3. The subject develops a cataract.

If a subject has been withdrawn from study drug treatment, the subject will be followed as described in Section 8.1.6, 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 all unused investigational product(s), request that the subject return for a Follow-up Visit, if applicable (see Section 8.1.6), 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.

9.5 Replacement of Subjects

Subjects who withdraw will not be replaced.

10 STUDY DRUG ADMINISTRATION AND MANAGEMENT

10.1 Method of Assigning Subjects to Treatment Groups

An interactive web or voice response system (IXRS) will be used to assign subjects to treatment sequence in a 1:1 ratio to receive either LUM/IVA during Treatment Period 1 and placebo during Treatment Period 2, or placebo during Treatment Period 1 and LUM/IVA during Treatment Period 2. The randomization code will be produced by Vertex Biostatistics or a qualified randomization vendor.

10.2 Packaging and Labeling

Vertex will supply the LUM 200 mg/IVA 125 mg fixed-dose combination tablets in weekly blister cards. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for LUM/IVA will be included in the Pharmacy Manual.

10.3 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	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)

10.4 Preparation and Dispensing

Study drug may be dispensed only under the supervision of the investigator or an authorized designee to the subject or the subject's legally appointed and authorized representative (e.g., parent or legal guardian) for administration to the subject. Study drug will be dispensed at study visits as appropriate.

For the visit at the end of each treatment period (i.e., the Week 8 and Week 24 Visits) and the ETT Visit (if applicable), subjects will be instructed to bring all remaining study drug to the site.

10.5 Dosage and Administration

Study drug tablets will be administered orally. During Treatment Period 1 and Treatment Period 2, subjects will take 2 tablets (LUM/IVA or matching placebo) twice per day.

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. All doses of study drug (morning and evening, as applicable) should be administered at approximately every 12 hours (± 2 hour) on each dosing occasion (e.g., if the morning doses of study drug are administered at 08:00 hours on Day 1, all subsequent morning doses should be administered between 06:00 hours and 10:00 hours).

2. At the first visit of each treatment period (i.e., on the Day 1 and Week 16 Visits), subjects whose FEV_1 at the Screening Visit was <40% of predicted will be observed for 4 hours after the morning dose of study drug.
3. At study visits during the treatment periods, 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.
4. If a subject's scheduled visit is to occur in the afternoon, the following guidelines must be used for administering either the morning or evening dose:
    - 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.

10.6 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 resume only after approval by the medical monitor. Specific instructions for interruption for elevated LFT levels are provided in Section 11.6.3.

10.7 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 authorized designee until inventoried by the study monitor. The study monitor will review study drug records and inventory throughout the study.

10.8 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. The site monitor will instruct the site when it is appropriate to return or destroy study drug. If the site monitor authorizes destruction at the study site, the investigator, or authorized designee, 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. Procedures for destruction or return of the study drug will be detailed in the Pharmacy Manual.

10.9 Compliance

To ensure treatment compliance, the investigator or authorized designee will supervise all study drug dosing that occurs at the site. At each visit, site personnel will review the subject's

compliance with study drug dosing and remind the subject of study drug dosing requirements. Compliance will also be assessed by ongoing study drug count.

10.10 Blinding and Unblinding

10.10.1 Blinding

This study is double-blind. The subjects and all site personnel, including the investigator, site monitor, and study team, will remain blinded to treatment assignments until database lock. Exceptions are made for the following personnel:

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

Vertex Quality Assurance Good Clinical Practice (GCP) personnel and all other Vertex Bioanalysis laboratory personnel will be blinded to the treatment assignment.

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.

10.10.2 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 an electronic process.

Unblinding of an 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 (MICC) 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. Contact information for the Vertex medical monitor and MICC will be provided in the Study Reference Manual.

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

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 schedule of assessments is shown in Table 3-1, Table 3-2, and Table 3-3.

[redacted]

Spirometry will be performed as described in Section 11.3.1.

Vital sign assessments will be performed before blood draws.

Liver function testing may be performed predose or postdose. At the Day 1 and Week 16 Visits, urine pregnancy tests must be negative before study drug is administered.

11.2 Subject Characteristics and Medical History

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

Medical history will be elicited from each subject during the Screening Period. Based on the medical history, the subject will be assessed for any disqualifying medical conditions as specified in the inclusion and exclusion criteria. The medical history will include a complete review of systems, past medical and surgical histories, and any allergies.

11.3 Efficacy

11.3.1 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines[26] at the time points noted in Table 3-1, Table 3-2, and Table 3-3 and according to the additional

guidelines that follow. (Spirometry on Day 2 and the day after the Week 16 Visit [if applicable] will be considered safety assessments and not efficacy assessments.)

Pre-bronchodilator spirometry is defined as spirometry testing performed for a subject who has

- withheld their short-acting β-agonist (e.g., albuterol) or anticholinergic (e.g., Atrovent®) for more than 4 hours before the spirometry assessment; **and**
- 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.

At the Screening Visit, spirometry may be performed pre- or post-bronchodilator. During the study, all spirometry assessments should be performed pre-bronchodilator. Spirometry assessments must be performed before the study drug dose at the visit. In the event that a subject forgets to withhold bronchodilators, spirometry should be performed according to the following:

- If the subject's Day 1 predose spirometry is obtained pre-bronchodilator, but on a subsequent visit the subject forgets to withhold the bronchodilator dose, a post-bronchodilator spirometry will be obtained for that visit only and the visit will not be rescheduled.
- If, at the subject's Day 1 predose spirometry assessment, the subject forgets to withhold the dose of bronchodilator, spirometry should be performed post-bronchodilator and all subsequent spirometric measurements during the study should be performed post-bronchodilator.
- Each spirometry assessment will be recorded in the source documents as pre-bronchodilator or post-bronchodilator.

At study visits that include administration of study drug, spirometry will be performed before dosing.

All sites will be provided with spirometers to be used for all study assessments. [redacted]. Lung function equipment in the participating centers will be equally calibrated according to the ATS/ERS guidelines for lung function testing.[27]

Spirometry data will be transmitted to a centralized spirometry service for quality review. [redacted]

[redacted]

11.6 Safety

11.6.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with International Conference on Harmonisation (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 case report form (CRF) completion guidelines as well as training for investigators will be provided.

11.6.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory, with the exception of urine pregnancy tests, which will be analyzed locally. Although blood samples are to be collected and analyzed at a central laboratory, a local laboratory may be used if a subject cannot return to the study site for the mandatory liver function testing (Section 11.6.3).

Laboratory test results that are abnormal and considered clinically significant will be recorded 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 at Screening	Liver Function Tests	Hematology at Screening
Glucose	Bilirubin, direct bilirubin	Hemoglobin
Blood urea nitrogen	Aspartate aminotransferase	Erythrocytes:
Creatinine	Alanine aminotransferase	Mean corpuscular hemoglobin
Sodium	Gamma glutamyl transpeptidase	Mean corpuscular hemoglobin concentration
Potassium	Alkaline phosphatase	Mean corpuscular volume
Calcium		Platelets
Chloride		Reticulocytes (absolute)
Magnesium		Leukocytes
Bicarbonate		Differential (absolute and percent):
Phosphate		Eosinophils
Bilirubin, direct bilirubin		Basophils
Alkaline phosphatase		Neutrophils
Aspartate aminotransferase		Lymphocytes
Alanine aminotransferase		Monocytes
Amylase		
Lactate dehydrogenase		
Lipase		
Gamma glutamyl transpeptidase		
Protein		
Albumin		
Creatine kinase		

Pregnancy Testing for Female Subjects of Childbearing Potential

Serum samples will be analyzed at the central laboratory. Urine beta-human chorionic gonadotropin tests will be performed at the study site. The urine pregnancy tests at Day 1 and Week 16 must be negative before the first dose of study drug.

If a urine pregnancy test is positive, all study drug dosing will stop and the pregnancy will be confirmed with a serum beta-human chorionic gonadotropin test. If the subject is pregnant, the procedures outlined in Section 11.6.7.2 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.

11.6.3 Elevation of Liver Function Test Parameters

Study Drug Interruption

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

- ALT or AST ≥5 × ULN
- ALT or AST ≥3 × ULN in association with 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 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 authorized designee is required before resumption of study drug. Upon resumption of study drug, transaminases should 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.

Mandatory Liver Function Testing

Liver function testing (ALT, AST, gamma glutamyl transpeptidase, alkaline phosphatase, and bilirubin) must be performed as shown in Table 3-2 and Table 3-3. These blood samples should 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).

11.6.4 Physical Examinations and Vital Signs

At the Screening Visit, a PE of all body systems will be performed. At other visits, symptom-directed PEs can be performed at the discretion of the investigator or healthcare provider.

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

Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be collected with the subject in a seated position after the subject has been at rest for at least 5 minutes. Blood pressure will be measured by sphygmomanometer.

11.6.5 Ophthalmologic Examination

Subjects who are less than 18 years of age at the Screening Visit will undergo an ophthalmologic examination during the Screening Period and at the Week 24 Visit, the ETT Visit, **or** the Follow-up Visit. These ophthalmologic examinations are not required under the following circumstances:

- If there is documentation of an ophthalmologic examination that met protocol criteria and was conducted within 3 months before the Screening Visit, the subject is not required to have a repeat ophthalmologic examination during the Screening Period.
- If the subject received study drug for a total of less than 4 weeks, the ophthalmologic examination at the Week 24, ETT, or Follow-up Visit is not required.

The ophthalmologic examination 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

These examinations must be conducted by a licensed ophthalmologist or optometrist.

If a cataract or lens opacity is identified and determined to be clinically significant by the ophthalmologist or optometrist, the subject (and the subject's parent/guardian if the subject is a minor) will be notified.

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

11.6.6 Ophthalmologic History

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

11.6.7 Contraception and Pregnancy

11.6.7.1 Contraception

The effects of LUM monotherapy or LUM/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.

Participation in this 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 participants of this study 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 following the last dose of study drug.

Definition of Childbearing Potential

All female subjects who have had their first menstrual period, from the time of the Screening Visit through the Follow-up Visit, including subjects with tubal ligations, will be considered to be of childbearing potential unless:

- The subject has had a documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy.
- The subject is postmenopausal, defined as at least 12 months of continuous spontaneous amenorrhea with serum FSH levels ≥40 mIU/L.

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 study drug.
- If the female is of non-childbearing potential, as defined above.

Acceptable Contraceptive Methods

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

- Vasectomy performed 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 a diaphragm, cervical cap, or female condom) with spermicide. Local regulations may require use of an additional acceptable method of contraception.
- Note: Hormonal contraceptives 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 (hormone-releasing or non-hormone-releasing) for at least 90 days.
- Barrier contraception (such as a 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

- A female condom cannot be used with a male condom (as a double method of contraception) due to risk of tearing.
- Male and female subjects who are not sexually active 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.

11.6.7.2 Pregnancy

Subjects will be counseled to inform the investigator of any pregnancy that occurs during study drug 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 during study participation, study drug must be permanently discontinued immediately. The investigator must notify the medical monitor and Vertex GPS 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 (and assent form, if applicable) will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

11.6.8 Pulse Oximetry

Arterial oxygen saturation by pulse oximetry will be measured at visits noted in Table 3-1 and Table 3-2. Pulse oximetry will be assessed after the subject has been at rest (seated or supine) for at least 5 minutes and before blood sample collection. The assessments of pulse oximetry on Day 2 and the day after the Week 16 Visit will be performed only for subjects whose FEV_1 at the Screening Visit is <40% of predicted. At these visits, pulse oximetry will be collected before the morning dose of study drug.

11.6.9 Spirometry

Spirometry assessments other than the assessments on Day 2 and the day after the Week 16 Visit will be considered efficacy assessments, as discussed in Section 11.3.1. The assessments of spirometry on Day 2 and the day after the Week 16 Visit will be considered safety assessments and not efficacy assessments. They will be performed only for subjects whose FEV_1 at the Screening Visit is <40% of predicted.

12 STATISTICAL AND ANALYTICAL PLANS

Analyses of efficacy and safety data will be described in a statistical analysis plan (SAP). The SAP will be finalized before database lock for the final analysis.

12.1 Sample Size and Power

No formal sample size calculation is conducted for this study of exploratory nature. The planned sample size of approximately 20 subjects is based on the number of subjects expected to be available for participation.

Assuming an estimated standard deviation (SD) of the paired differences of 8.00 in $ppFEV_1$, the available sample size of 20 subjects produces a two-sided 95% CI of the mean treatment difference with precision (margin of error) of 3.74 percentage points. In addition, Table 12-1 displays a list of treatment differences detectable under various scenarios of power and significance level, with total sample sizes of 15 and 20.

Table 12-1 Difference Detectable Under Various Scenarios of Power, Alpha, and N

Power	90%	90%	90%	90%	80%	80%	80%	80%
Alpha	10%	10%	5%	5%	10%	10%	5%	5%
N	20	15	20	15	20	15	20	15
Difference detectable	5.4	6.4	6.1	7.3	4.6	5.4	5.3	6.3

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 efficacy analyses.

The Safety Set is defined as all subjects who received at least 1 dose of study drug. The Safety Set will be used for safety analyses.

12.3 Statistical Analysis

This section summarizes the planned statistical analyses for this study. The Vertex Biometrics department or a designated CRO will conduct these analyses. SAS® Version 9.2 or higher will be used to generate all statistical outputs (tables, figures, listings, and data sets).

For each Treatment Period, subjects will be categorized according to the treatment they actually received, whether or not it corresponds to the treatment to which they were assigned.

12.3.1 General Considerations

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

Categorical variables will be summarized using counts and percentages.

Unless specified otherwise, only descriptive analyses will be performed (i.e., no statistical hypothesis testing will be performed).

Baseline: Study baseline is defined as the most recent nonmissing measurement collected before the first administration of study drug in Treatment Period 1. Period baseline is defined as the most recent nonmissing measurement collected before the first administration of study

drug in each treatment period. For Treatment Period 1, the period baseline will be the study baseline; for Treatment Period 2, the period baseline will be from an assessment measured after the Washout Period.

For all efficacy analyses, the statistical inference will be based on change from study baseline. However, efficacy analyses based on change from period baseline will also be presented. Similarly, summary tables, as applicable, will be presented based on both baselines.

All subject data, including those derived, will be presented in the subject data listings; listings will display all subjects who were randomized, regardless of whether or not they received study drug.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

The number and percentage of subjects in each disposition category (e.g., randomized, included in the FAS, included in the Safety Set, completed each treatment period, completed the Follow-up Visit, and discontinued study, with reasons for discontinuation) will be summarized by treatment sequence and overall.

12.3.2.2 Demographics and Baseline Characteristics

The following demographics and baseline characteristics for the FAS will be summarized by treatment sequence and overall: age, sex, race, weight, height, BMI, weight z-score, and BMI z-score.

12.3.2.3 Prior and Concomitant Medications

Medications taken from 30 days before the Screening Visit up to the Follow-up Visit will be summarized by preferred term using the World Health Organization-Drug Dictionary Enhanced for the FAS as frequency tables in 2 parts:

- Prior medication: medication that started before the first dose of study drug, regardless of when dosing of the medication ended.
- Concomitant medication: medication received at or after the first dose of study drug, medication that was received before initial dosing and continued after initial dosing of study drug, or medication with missing stop date.

Medication that started before the first dose of study drug and continued after the first dose of study drug will be summarized as prior medication and separately as concomitant medication. Medications with a missing start date will be considered to have a start date before the first dose of study drug.

Prior medications will be summarized by treatment sequence, and concomitant medications will be summarized by treatment group.

12.3.2.4 Study Drug Exposure and Compliance

Exposure to study drug and dosing compliance will be summarized for the FAS by means of summary statistics.

Dosing compliance will be summarized for each treatment period for the FAS, and is calculated as the actual number of dosing occasions at which study drug was administered, as a percentage of the planned number of dosing occasions.

12.3.3 Efficacy Analysis

Efficacy analyses will be based on the FAS unless noted otherwise.

All efficacy data will be presented in subject data listings.

12.3.3.1 Change from Baseline in ppFEV1

The analysis of absolute change from baseline in $ppFEV_1$ through 8 weeks of study drug treatment will be based on a mixed-effects model for repeated measures (MMRM) utilizing the FAS.

The model will include the absolute change from the study baseline in each treatment period as the dependent variable; sequence, treatment, treatment period, and visit within treatment period as fixed effects; $ppFEV_1$ at study baseline as a covariate; and subject nested within sequence as the random effect. An unstructured covariance matrix is further assumed for the repeated measurements of the same subject within each treatment period. If there is a convergence problem for the unstructured covariance matrix, an appropriate covariance matrix structure, such as compound symmetry, will be assumed in the primary analysis. The estimated mean treatment difference overall, a 95% CI, and a 2-sided *P* value will be provided. The estimated mean treatment difference at each visit along with the corresponding 95% CI and *P* value will also be presented. Raw values and changes from baseline will be summarized by treatment group using descriptive statistics. Paired *t*-tests for difference between treatments for each subject, as well as Wilcoxon signed-rank tests, may be provided.

As a supportive analysis, the analysis will be repeated using change from period baseline instead of change from study baseline.

Summary, plots, and individual listings of efficacy data will be generated. A more detailed description of the planned statistical analysis of efficacy endpoints will be presented in the SAP.

[redacted]

[redacted]

12.3.5 Safety Analysis

The overall safety profile of LUM/IVA will be assessed in terms of:

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (LFTs)
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature)

Safety analyses will be based on the Safety Set.

All safety data will be presented in subject data listings.

12.3.5.1 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing an AE will be summarized by the MedDRA system organ class and preferred term. AEs will be classified as pre-treatment or treatment-emergent.

Pre-treatment 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 Follow-up Visit.

Only TEAEs will be summarized in tables. Some rules that will apply to the summarization of AEs are (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.

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

12.3.5.2 Clinical Laboratory Assessments

All statistical summaries of laboratory values will be provided using SI units. LFT results will be summarized by treatment group at each scheduled time point. Changes from baseline will also be summarized. Maximum shift changes from baseline based on the LFT normal ranges will be tabulated by treatment. A subject data listing of abnormal LFT values from scheduled and unscheduled time points will be provided. A listing of all laboratory values of Grade 3 toxicity or worse will also be provided. Results for hematology and chemistry assessments will be listed and summarized. Clinically significant abnormal laboratory findings will be reported as AEs.

12.3.5.3 Vital Signs

Systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), respiratory rate (breaths per minute), and body temperature (degrees C) will be summarized by treatment. Changes from baseline will also be summarized. Clinically significant abnormal findings will be reported as AEs.

12.3.5.4 Physical Examination

PE results performed as part of the Screening Period assessment will be presented in subject data listings only. Clinically relevant results identified after screening will be reported as AEs.

12.3.6 Interim Analysis

No interim analysis is planned.

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 and vital signs, will be assessed, and those deemed a clinically significant worsening from baseline will be documented as AEs. 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 clinical status of the subject indicates a life-threatening AE.

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time the 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 Follow-up Visit: through the Follow-up Visit
- For enrolled subjects who do not have a Follow-up Visit, the **earliest** of:
  - 28 days after the last dose of study drug, or
  - the ETT Visit, if that visit is 3 weeks or later after the last dose of study drug (see Section 8.1.6).

All subjects will be queried, using non-leading 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 August 2015). AEs of CTCAE Grade 4 and Grade 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 experience 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 record).

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 (or the subject's parent/guardian) signed the ICF, and the hospitalization or procedure was planned before the signing of 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 Follow-up Visit, regardless of causality, will be reported by the investigator to Vertex GPS. In addition, all SAEs that occur after the 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 Clinical Trials 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 Vertex Clinical Trials 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 Vertex Clinical Trial 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 Global Patient Safety via
Email: [redacted] (Preferred Choice)
Or via 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 independent ethics committees (IECs).

It is the responsibility of the investigator or designee to promptly notify the local institutional review board (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 Guidelines and all applicable laws and regulations and will be subject to approval by Vertex or its authorized 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 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 doctor 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.

13.2.6 Record Retention

The investigator will maintain all study records according to ICH GCP Guidelines and/or applicable local regulatory requirements, 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 authorized designee. Monitoring will be done by personal visits from a representative of Vertex, or authorized 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 #: VX15-809-111	Version #: 2.0	Version Date 17 February 2017
Study Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Efficacy of Lumacaftor/Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis Who Have an *A455E-CFTR* Mutation		

This Clinical Trial Protocol has been reviewed and approved by the sponsor.

15.2 Investigator Signature Page

Protocol #: VX15-809-111	Version #: 2.0	Version Date 17 February 2017
Study Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Efficacy of Lumacaftor/Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis Who Have an *A455E-CFTR* Mutation		

I have read Protocol VX15-809-111, Version 2.0 and agree to conduct the study according to its terms. I understand that all information concerning LUM/IVA and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date