1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3, Rollover Study to Evaluate the Safety of Long-term Treatment With Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

Vertex Study Number: VX16-809-116

[redacted]

Date of Protocol: 10 October 2016 (Version 1.1)

Vertex Pharmaceuticals Incorporated
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2 PROTOCOL SYNOPSIS

Title A Phase 3, Rollover Study to Evaluate the Safety of Long-term Treatment With Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

Brief Title A Rollover Safety Study of Lumacaftor/Ivacaftor in Subjects Aged 2 Years and Older With Cystic Fibrosis, Homozygous for *F508del*

Clinical Phase and Clinical Study Type Phase 3 safety

Objectives

Primary Objective

To evaluate the long-term safety of lumacaftor/ivacaftor (LUM/IVA) combination therapy in subjects aged 2 years and older with cystic fibrosis (CF), homozygous for *F508del*

Secondary Objective

To evaluate the pharmacodynamics (PD) of long-term LUM/IVA combination therapy in subjects aged 2 years and older with CF, homozygous for *F508del*

Endpoints

Primary Endpoint

Safety and tolerability assessments based on adverse events (AEs), changes in clinical laboratory values, electrocardiograms (ECGs), vital signs, pulse oximetry, ophthalmological examinations (OEs), and spirometry

Secondary Endpoints

The following endpoints will be analyzed using baseline values in the previous study (i.e., Study VX15-809-115 Part B [Study 115B]):

- Absolute change from baseline in sweat chloride
- Absolute change from baseline in body mass index (BMI) and BMI-for-age z-score
- Absolute change from baseline in weight and weight-for-age z-score
- Absolute change from baseline in stature and stature-for-age z-score
- Time-to-first pulmonary exacerbation from baseline
- Number of pulmonary exacerbations from baseline
- Number of CF-related hospitalizations from baseline
- Absolute change from baseline in fecal elastase-1 (FE-1) levels
- Absolute change from baseline in serum levels of immunoreactive trypsinogen (IRT)
- Change from baseline in microbiology cultures
- Absolute change from baseline in lung clearance index $(LCI)_{2.5}$
- Absolute change from baseline in $LCI_{5.0}$

[redacted]

Number of Subjects

Approximately 56 subjects are potentially eligible to be enrolled

Study Population

Treatment Cohort

Male and female subjects who completed LUM/IVA treatment and the Safety Follow-up Visit in Study 115B

Observational Cohort

Male and female subjects who received at least 4 weeks of LUM/IVA treatment in Study 115B and completed visits up to Week 24 and the Safety Follow-up Visit, if required, in Study 115B, but do not meet eligibility criteria for enrollment in the Treatment Cohort or who choose not to enroll in the Treatment Cohort

Investigational Drug

Active Substance: LUM/IVA fixed-dose combination

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

Strength and Route of Administration

- LUM 100-mg/IVA 125-mg granules for oral administration
- LUM 150-mg/IVA 188-mg granules for oral administration
- LUM 100-mg/IVA 125-mg tablets for oral administration

Doses Investigated

Subjects 2 through 5 years of age at enrollment

- LUM 100 mg/IVA 125 mg every 12 hours (q12h) for subjects weighing <14 kg at enrollment
- LUM 150 mg/IVA 188 mg q12h for subjects weighing ≥14 kg at enrollment

Notes: Doses may be adjusted upward for changes in weight and age. Doses above are those planned for Study 115B. Based on results from Study 115A and 115B, doses for subjects <6 years of age in Study VX16-809-116 (Study 116) may be modified.

Subjects ≥6 years of age at enrollment

LUM 200 mg/IVA 250 mg q12h (2 × LUM 100-mg/IVA 125-mg tablet q12h)

Study Duration

Treatment Cohort

Up to 98 weeks (96 weeks for the Treatment Period and 2 weeks for safety follow-up, if applicable)

Observational Cohort

96 weeks

Study Design

The Treatment Cohort includes the following:

- Treatment Period (Day 1 through Week 96; the last dose of study drug is the dose before the Week 96 Visit).
- Safety Follow-up Visit (2 weeks ± 4 days after the last dose of LUM/IVA)

The Observational Cohort includes 2 long-term follow-up telephone contacts at Week 48 and Week 96.

Assessments

Treatment Cohort

Safety: AEs, clinical laboratory values (serum chemistry, hematology, coagulation, and urinalysis), ECGs, vital signs, pulse oximetry, physical examinations, spirometry (subjects ≥3 years old at screening in Study 115B), and OEs

Pharmacodynamics: Sweat chloride, BMI/BMI-for-age z-score, weight/weight-for-age z-score, stature/stature-for-age z-score, spirometry (subjects ≥3 years old at screening in Study 115B), pulmonary exacerbations, CF-related hospitalizations, FE-1, IRT, qualitative microbiology cultures, and LCI (subjects ≥3 years old at screening in Study 115B who consent/assent to the optional LCI Substudy in Study 115B and Study 116)

Observational Cohort

Safety: Serious adverse events (SAEs)

Statistical Analyses

Approximately 56 subjects are potentially eligible to be enrolled. Assuming a 10% dropout rate in Study 115B, 50 subjects are expected to be enrolled in Study 116.

Treatment Cohort

The analysis will be performed over the Cumulative Study Period.

Safety Analysis

All treatment-emergent AE (TEAE) summaries will be described using the incidence of TEAEs and number of events per 100 patient-years (number of events adjusted for the total duration of exposure) for the Cumulative Study Period.

Continuous safety endpoints will be summarized descriptively at each visit during the Cumulative Study Period.

For the categorical laboratory, vital, and ECG variables, the number and percentage of subjects in each category during the Treatment-emergent Period of the Cumulative Study Period will be summarized.

The safety analysis for the Cumulative Study Period will be based on the Safety Set, which will include all subjects who received at least 1 dose of study drug in Study 115B.

Pharmacodynamic Analysis

For all continuous PD endpoints, raw values and absolute change from Cumulative Study Baseline at each visit in the Cumulative Study Period will be summarized based on the Full Analysis Set (FAS), which includes all subjects who were enrolled and exposed to any amount of study drug in Study 115B.

Time-to-first pulmonary exacerbation will be estimated using the Kaplan-Meier method based on the FAS for the Cumulative Study Period.

The number of pulmonary exacerbations starting during the Cumulative Study Period normalized by the time spent in the Cumulative Study Period will be summarized.

The number of CF-related hospitalizations through last visit will be summarized similarly.

Observational Cohort

Listings will be provided for SAEs in Study 116 based on all subjects enrolled in the Observational Cohort.

IDMC Reviews

An independent data monitoring committee (IDMC) will be formed using the Cystic Fibrosis Foundation Data Safety Monitoring Board. The IDMC objectives and operational details will be defined in a separate document (IDMC Charter), which will be finalized before the first subject is enrolled. The IDMC will conduct regular planned reviews of study data for the purpose of safety monitoring as outlined in the IDMC Charter.

3 SCHEDULE OF ASSESSMENTS

3.1 Treatment Cohort

Table 3-1 Study VX16-809-116: Treatment Cohort - Treatment Period and Safety Follow-up Visit

	Treatment Period					ETT Visit[b]	Safety Follow-up Visit[c]
Event/Assessment[a]	**Day 1[d]**	**Day 3 (± 1 Day)**	**Day 15 (± 3 Days)**	**Weeks 12, 24, 36, 48, 60, 72, 84 (± 7 Days)**	**Week 96 (± 7 Days)**	**As Soon as Possible After the Last Dose**	**2 Weeks (± 4 Days) After the Last Dose**
Informed consent/assent	X						
Clinic visit	X		X	X	X	X	X
Telephone contact[e]		X					
Stature and weight[f]	X		X	X	X	X	X
Vital signs[g]	X[h]		X	X	X	X	X
Pulse oximetry[g]	X		X	X	X	X	X
OEs[i]	X			Week 48[j]	X[j,k]	X[j,k]	X[j,k]
Full PE[l]	X			Weeks 24, 48, 72	X	X	X
Abbreviated PE	X[m]						

[a] Assessments will be performed before LUM/IVA dosing unless noted otherwise.

[b] If the ETT Visit occurs 10 days or later after the last dose of LUM/IVA, the Safety Follow-up Visit will not be required (Section 9.1.2.3). Subjects who prematurely discontinue LUM/IVA treatment for AEs should be followed until the AE is considered resolved.

[c] The Safety Follow-up Visit is required for 1) subjects who complete their ETT Visit <10 days after the last dose of LUM/IVA (footnote b and Section 9.1.2.3); and 2) subjects who interrupt LUM/IVA treatment and complete their Week 96 Visit <10 days after the last dose of LUM/IVA; it is not required for subjects who continue onto commercially-available, physician-prescribed LUM/IVA within 2 weeks (± 4 days) of completing LUM/IVA treatment at the Week 96 or ETT Visit.

[d] For subjects at sites activated by the time of their Study 115B Safety Follow-up Visit, their Study 116 Day 1 Visit will be on the same day as their Study 115B Safety Follow-up Visit, and any Study 116 Day 1 assessments that were specified to be performed at the Study 115B Safety Follow-up Visit do not need to be repeated. If the Study 116 Day 1 Visit does not coincide with the subject's Study 115B Safety Follow-up Visit, the subject will complete all Study 116 Day 1 assessments (except the OE if it was performed within the last 3 months before the visit). See Section 9.1.1 for details.

[e] Telephone contacts will be made to assess the subject's status, any AEs, medications, treatments, and procedures.

[f] If subjects can stand unassisted and follow directions, stature should be measured as height; otherwise, stature will be measured as length. Stature and weight must be measured with shoes off and while wearing light clothing. BMI will be derived from this assessment. See Section 11.4.3 for details.

[g] The subject should rest for at least 5 minutes before having vital signs and pulse oximetry measured. See Section 11.6.4 for details.

[h] Vital signs will be measured predose and at 1 hour (± 15 minutes), 2 hours (± 15 minutes), and 4 hours (± 15 minutes) postdose on Day 1.

[i] An OE will be conducted by a licensed ophthalmologist. Subjects with documentation of bilateral lens removal do not need the OE. See Section 11.6.6 for details.

[j] Subjects may complete the OE within ± 1 week of the scheduled visit.

[k] An OE will be conducted at the Week 96 Visit (or the ETT Visit if the subject does not have a Week 96 Visit, unless the discontinuation is due to initiation of treatment with commercially-available LUM/IVA), or the Safety Follow-up Visit.

[l] Symptom-directed PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator. See Section 11.6.4 for details.

[m] An abbreviated PE will be performed 4 hours (± 30 minutes) postdose on Day 1. See Section 11.6.4 for details.

Table 3-1 Study VX16-809-116: Treatment Cohort - Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period					ETT Visit[b]	Safety Follow-up Visit[c]
	Day 1[d]	Day 3 (± 1 Day)	Day 15 (± 3 Days)	Weeks 12, 24, 36, 48, 60, 72, 84 (± 7 Days)	Week 96 (± 7 Days)	As Soon as Possible After the Last Dose	2 Weeks (± 4 Days) After the Last Dose
Standard 12-lead ECGs[n]	X		X	Week 48	X	X	X
Serum chemistry[o]	X		X	Weeks 12, 24, 36, 48, 72	X	X	X
Hematology[o]				Weeks 12, 24, 36, 48, 72	X	X	X
Coagulation studies[o]				Week 48	X		
Urinalysis[o]	X			Week 48	X		
Qualitative microbiology cultures[p]	X			Weeks 24, 48, 72	X	X	
Immunoreactive trypsinogen	X			Week 48	X		X
Fecal elastase-1[q]	X			Week 48	X		X
Sweat chloride[r]	X			Weeks 24, 48	X		X
LCI (optional)[s]	X			Weeks 24, 48	X		X
Spirometry[t]	X[u]		X	Weeks 24, 48	X	X	X
Other events related to outcome[v]	X		X	X	X	X	X
LUM/IVA dosing[w]	**LUM/IVA q12h**						
Observation 4 hours after the first dose	X						
Study drug count	X		X	X	X	X	

[n] A standard 12-lead ECG will be performed. The subject will be instructed to rest in the supine position for at least 5 minutes, if possible, before having an ECG performed. The ECG will be performed before any other procedures that may affect heart rate, such as blood draws. See Section 11.6.5 for details.

[o] See Section 11.6.2 for details.

[p] See Section 11.4.7 for details.

[q] Samples will be collected at the study center during the study visit; however, samples may be collected by the subject up to 24 hours before the study visit (e.g., at home) and brought to the study visit (Section 11.4.5). The sample may be collected pre- or postdose.

[r] The sweat chloride test will be conducted at approximately the same time as predose blood collections. At each time point, 2 samples will be collected, 1 sample from each arm (left and right). See Section 11.4.1 for details.

[s] The LCI assessment (only subjects who are ≥3 years of age at Study 115B screening who consent/assent to the optional LCI Substudy in Study 115B and Study 116) should be performed pre-bronchodilator. See Sections 11.1 and 11.4.2 for details. The assessment will be performed in multiple replicates and before the spirometry assessment.

[t] Spirometry (only subjects who are ≥3 years of age at Study 115B screening) should be performed pre-bronchodilator. See Sections 11.1 and 11.6.7 for details.

[u] Day 1 spirometry will be performed before LUM/IVA dosing and at 2 hours (± 30 minutes) and 4 hours (± 30 minutes) postdose.

[v] Other events related to outcome include assessments relating to pulmonary exacerbations, administration of antibiotic therapy for sinopulmonary signs or symptoms, and hospitalizations (Section 11.4.4).

[w] LUM/IVA will be administered q12h (± 2 hours) within 30 minutes of consuming fat containing food (Section 9.6). On days of scheduled visits, the dose will be administered at the site after predose assessments have been completed. The last dose will be the dose administered before the Week 96 Visit. See Section 9.6 for dose determination details.

Table 3-1 Study VX16-809-116: Treatment Cohort - Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period					ETT Visit[b]	Safety Follow-up Visit[c]
	Day 1[d]	Day 3 (± 1 Day)	Day 15 (± 3 Days)	Weeks 12, 24, 36, 48, 60, 72, 84 (± 7 Days)	Week 96 (± 7 Days)	As Soon as Possible After the Last Dose	2 Weeks (± 4 Days) After the Last Dose
Medications, treatments, and procedures review	Continuous from signing of ICF through Safety Follow-up Visit (if required)						
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit (if required)						

AE: adverse event; BMI: body mass index; ECG: electrocardiogram; ETT: Early Termination of Treatment; ICF: informed consent form; IVA: ivacaftor; LCI: lung clearance index; LUM: lumacaftor; OE: ophthalmological examination; PE: physical examination; q12h: every 12 hours

3.2 Observational Cohort

Table 3-2 Study VX16-809-116: Observational Cohort

Event/Assessment	Day 1[a]	Long-term Follow-up Telephone Contact Weeks 48 and 96 (± 4 weeks)	Early Termination Telephone Contact[b]
Informed consent/assent	X		
Clinic visit	X		
Telephone contact		X	X
Serious adverse events	Continuous from signing of ICF through Week 96 or Early Termination Telephone Contact		

ICF: informed consent form; IVA: ivacaftor; LUM: lumacaftor

[a] For subjects at sites activated by the time of their applicable Study 115B visit (i.e., the Week 24 Visit or the Safety Follow-up Visit, if required), their Study 116 Day 1 Visit will be the same day as their applicable Study 115B visit, and any Study 116 Day 1 assessments that were specified to be performed at the applicable Study 115B visit do not need to be repeated. If the Study 116 Day 1 Visit does not coincide with the subject's applicable Study 115B visit, the subject will complete all Study 116 Day 1 assessments. See Section 9.1.1 for details.

[b] Subjects who become eligible to receive commercially-available, physician-prescribed LUM/IVA, and who choose to continue onto commercially-available LUM/IVA, must have an Early Termination Telephone Contact to terminate study participation.

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomic class
BMI	body mass index
CF	cystic fibrosis
CFTR	*CF transmembrane conductance regulator* gene
CFTR	CF transmembrane conductance regulator protein
CI	confidence interval
Cl^-	chloride ion
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
ETT	early termination of treatment
EU	European Union
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F508del	CFTR protein lacking the phenylalanine normally found at position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FE-1	fecal elastase-1
$FEF_{25-75\%}$	forced expiratory flow, midexpiratory phase
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLI	Global Lung Function Initiative
GPS	Global Patient Safety
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IRB	institutional review board
IRT	immunoreactive trypsinogen
IV	intravenous
IVA	ivacaftor
LCI	lung clearance index

Abbreviation	Definition
$LCI_{2.5}$	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value
$LCI_{5.0}$	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value
LFT	liver function test
LLN	lower limit of normal
LUM	lumacaftor
MBW	multiple-breath washout
MedDRA	Medical Dictionary for Regulatory Activities
OE	ophthalmological examination
P	probability
PD	pharmacodynamics(s)
PE	physical examination
PK	pharmacokinetic(s)
$ppFEV_1$	percent predicted FEV_1
PR	PR interval
PT	preferred term
q12h	every 12 hours
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
RR	interval from the onset of 1 QRS complex to the next
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SI	SI units (International System of Units)
SOC	system organ class
SUSAR	suspected, unexpected, serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States

5 INTRODUCTION

5.1 Background

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 approximately 70,000 individuals worldwide,[1] with approximately 30,000 individuals in the US.[1,2] 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.[2-4] Although the disease affects multiple organs, progressive loss of lung function is the leading cause of mortality.[5]

CF is caused by a defect in the gene encoding CFTR, an epithelial chloride (Cl^-) ion channel that is responsible for aiding in the regulation of salt and water absorption and secretion in various tissues.[6] This function is defective in patients with CF due to a loss of cell surface expression and/or function of CFTR.

Lumacaftor (LUM; VX-809)/ivacaftor (IVA; VX-770) combination therapy (Orkambi™) is the first medicine designed to treat the underlying molecular defect and enhance the function of CFTR in patients homozygous for *F508del*. Orkambi is approved in the US for patients 6 years and older who are homozygous for *F508del*, and in the EU, Canada, Australia, and Switzerland for patients 12 years and older who are homozygous for *F508del*. The LUM/IVA development program is designed to support the hypothesis that an oral chronic treatment restoring CFTR function can lead to improved pulmonary and extrapulmonary manifestations of CF, prevent progressive lung damage, and ultimately prolong survival.

Details about the LUM/IVA development program can be found in the Investigator's Brochure.[7]

5.2 Study Rationale

Approximately half of the total CF patient population is <18 years of age.[8] Even before the widespread adoption of newborn screening, the majority of patients with CF were diagnosed in infancy or early childhood due to manifestations of the disease. Pancreatic destruction leading to pancreatic exocrine insufficiency begins in utero, and lung involvement is manifest by pulmonary inflammation and infection that begins shortly after birth.

The primary objectives of Study VX15-809-115 (Study 115) are to obtain pharmacokinetic (PK) and safety information to support a proposed indication expansion of LUM/IVA in subjects aged 2 through 5 years, homozygous for *F508del*. The primary objective of Study VX16-809-116 (Study 116) is to evaluate the long-term safety of LUM/IVA in subjects aged 2 years and older with CF, homozygous for *F508del*, who participated in Study 115.

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the long-term safety of LUM/IVA combination therapy in subjects aged 2 years and older with CF, homozygous for *F508del*

6.2 Secondary Objective

To evaluate the pharmacodynamics (PD) of long-term LUM/IVA combination therapy in subjects aged 2 years and older with CF, homozygous for *F508del*

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Safety and tolerability assessments based on adverse events (AEs), changes in clinical laboratory values, electrocardiograms (ECGs), vital signs, pulse oximetry, ophthalmological examinations (OEs), and spirometry

7.2 Secondary Endpoints

The following endpoints will be analyzed using baseline values in the previous study (i.e., Study 115 Part B [Study 115B]):

- Absolute change from baseline in sweat chloride
- Absolute change from baseline in body mass index (BMI) and BMI-for-age z-score
- Absolute change from baseline in weight and weight-for-age z-score
- Absolute change from baseline in stature and stature-for-age z-score
- Time-to-first pulmonary exacerbation from baseline
- Number of pulmonary exacerbations from baseline
- Number of CF-related hospitalizations from baseline
- Absolute change from baseline in fecal elastase-1 (FE-1) levels
- Absolute change from baseline in serum levels of immunoreactive trypsinogen (IRT)
- Change from baseline in microbiology cultures
- Absolute change from baseline in lung clearance index $(LCI)_{2.5}$
- Absolute change from baseline in $LCI_{5.0}$

[redacted]

8 STUDY POPULATION

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

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for the study.

8.1 Inclusion Criteria

1. Subject's legally appointed and authorized representative (e.g., parent or legal guardian) will sign and date an informed consent form (ICF) and the subject will sign and date an assent form (if applicable).

2. Subjects entering the **Treatment Cohort** must meet the following criteria:
    - Completed 24 weeks of LUM/IVA treatment and the Safety Follow-up Visit in Study 115B
        - Subjects who had study drug interruptions are eligible if they completed study visits up to the Safety Follow-up Visit of Study 115B. Subjects who are not taking LUM/IVA at the end of the Study 115B Treatment Period (i.e., Week 24), including subjects who have LUM/IVA treatment temporarily interrupted as of Day 1 in Study 116, must receive Vertex approval for enrollment in the Treatment Cohort.

    Subjects entering the **Observational Cohort** must meet 1 of the following criteria:

    - Completed 24 weeks of LUM/IVA treatment and the Safety Follow-up Visit in Study 115B, but do not want to enroll in the Treatment Cohort.
    - Received at least 4 weeks of LUM/IVA treatment and completed visits up to Week 24 and the Safety Follow-up Visit, if required, of Study 115B but are not taking LUM/IVA at the end of the Study 115B Treatment Period (i.e., Week 24) because of a drug interruption and either did not receive Vertex approval to enroll in the Treatment Cohort or do not want to enroll in the Treatment Cohort.
    - Permanently discontinued LUM/IVA in Study 115B after receiving at least 4 weeks of treatment and remained in the study from the time of treatment discontinuation through the Week 24 Visit and Safety Follow-up Visit, if required.
3. Willing to remain on a stable CF medication regimen through the Safety Follow-up Visit (Treatment Cohort only).
4. As deemed by the investigator, the subject's legally appointed and authorized representative (e.g., parent or legal guardian) must be able to understand protocol requirements, restrictions, and instructions. The subject's legally appointed and authorized representative should be able to ensure that the subject will comply with, and is likely to complete, the study as planned.

8.2 Exclusion Criteria (Treatment Cohort Only)

1. Prematurely discontinued LUM/IVA treatment in Study 115B.
2. History of any comorbidity or laboratory abnormality that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering LUM/IVA to the subject (e.g., cirrhosis with portal hypertension).
3. History of drug intolerance or other serious reactions to LUM/IVA in Study 115B that would pose an additional risk to the subject in the opinion of investigator, and which should be discussed with the Vertex medical monitor.
4. Subjects with a history of allergy or hypersensitivity to LUM/IVA.
5. Liver function test (LFT) abnormality meeting criteria for LUM/IVA treatment interruption at the completion of Study 115B, for which no convincing alternative etiology is identified.
6. QTc value at the completion of Study 115B that would pose an additional risk to the subject in the opinion of investigator, and which should be discussed with the Vertex medical monitor (e.g., remained above the threshold value [>45 msec from baseline or >500 msec] on

repeated measurement or was noted on 2 or more occasions with no identified alternative etiology for the increased QTc).

7. History of poor compliance with LUM/IVA and/or procedures in Study 115B as deemed by the investigator.
8. Participation in an investigational drug trial (including studies investigating LUM and/or IVA) other than Study 115B. NOTE: participation in a non-interventional study is permitted (including observational studies, registry studies, and studies requiring blood collections without administration of study drug).

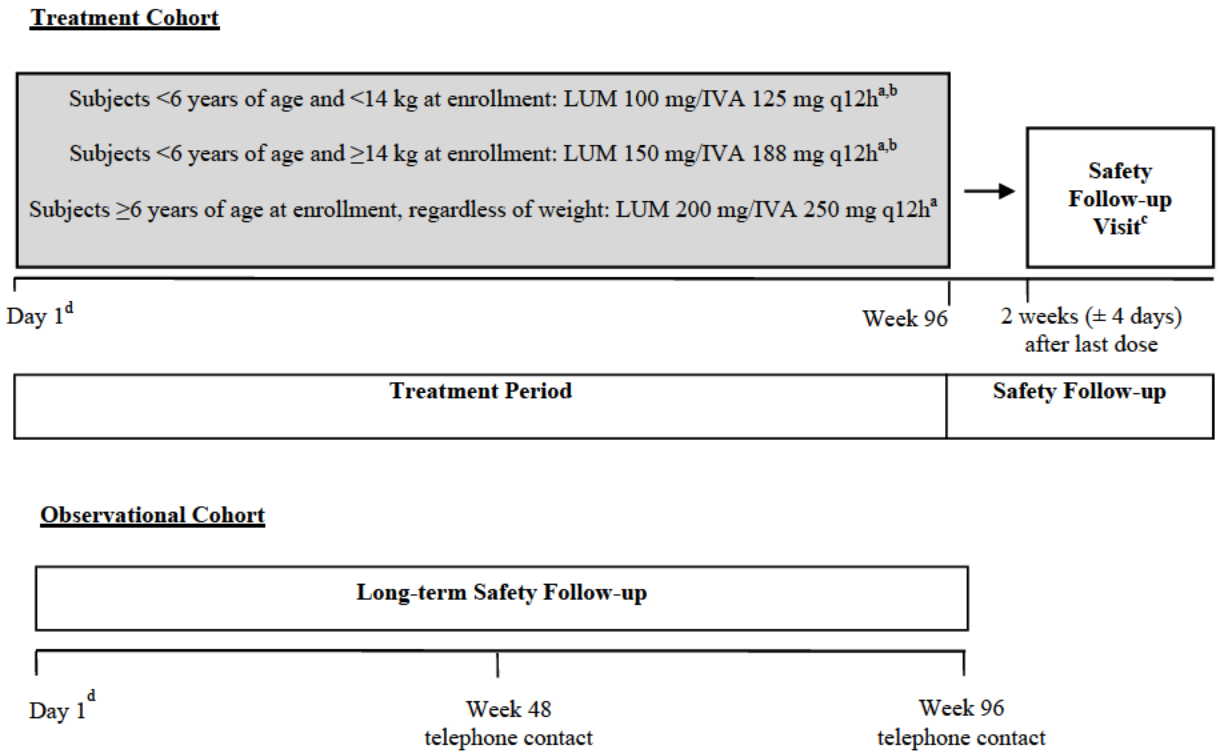
9 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 3, open-label, multicenter study with a Treatment Cohort and an Observational Cohort (Figure 9-1).

Procedural details are described in Sections 9.1.1 and 9.1.3.

Figure 9-1 Schematic of Study Design



ETT: Early Termination of Treatment; IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours

[a] Doses may be adjusted upward for changes in weight and age. See the rules for dose adjustments in Section 9.6.

[b] Doses are those planned for Study 115B. Based on results from Study 115A and 115B, doses for subjects <6 years of age in Study 116 may be modified.

[c] The Safety Follow-up Visit is required for 1) subjects who complete their ETT Visit <10 days after the last dose of LUM/IVA (Section 9.1.2.3); and 2) subjects who interrupt LUM/IVA treatment and complete their Week 96 Visit <10 days after the last dose of LUM/IVA; it is not required for subjects who continue onto commercially-available, physician-prescribed LUM/IVA within 2 weeks (± 4 days) of completing LUM/IVA treatment at the Week 96 or ETT Visit.

[d] See Section 9.1.1 for details regarding the timing of the Day 1 Visit.

9.1.1 Timing of Study 116 Day 1 Visit

9.1.1.1 Treatment Cohort and Observational Cohort

For subjects at sites activated by the time of their applicable Study 115B visit (i.e., the Safety Follow-up Visit for subjects in the Treatment Cohort and the Week 24 Visit or the Safety Follow-up Visit, if required, for subjects in the Observational Cohort), their Study 116 Day 1 Visit will be on the same day as their applicable Study 115B visit, and any Study 116 Day 1 assessments that were specified to be performed at the applicable Study 115B visit do not need to be repeated. If the Study 116 Day 1 Visit does not coincide with the subject's applicable Study 115B visit, the subject will complete all Study 116 Day 1 assessments (except the OE if it was performed within the last 3 months before the visit for subjects in the Treatment Cohort).

9.1.1.2 Treatment Cohort

Subjects at sites activated by the time of their applicable Study 115B visit (Section 9.1.1.1) may return within 1 calendar day to complete the remaining Day 1 assessments specific to Study 116 (including administration of the Day 1 dose). Predose vital sign and spirometry assessments must be repeated before dosing on the following calendar day.

Subjects who were enrolled but had Day 1 LUM/IVA administration procedures (Section 9.6) delayed more than 1 calendar day will repeat all assessments that were specified to be performed at the Day 1 visit before receiving their first dose of LUM/IVA (except for the OE if it was performed within the last 3 months before the visit).

9.1.2 Treatment Cohort

9.1.2.1 Treatment Period

To prepare for study participation, subjects will be instructed on the study restrictions (Section 9.4).

Treatment Period assessments are listed in Table 3-1. Subjects will be outpatients during the Treatment Period. All visits should occur within the windows specified.

The Treatment Period is 96 weeks; LUM/IVA will be administered every 12 hours (q12h) from Day 1 through Week 96. The dose before the Week 96 Visit will be the last dose. Administration and management details are provided in Sections 9.6 and 10.

Procedures for subjects who prematurely discontinue LUM/IVA treatment are described in Section 9.1.2.3.

9.1.2.2 Follow-up

The Safety Follow-up Visit is required for 1) subjects who complete their Early Termination of Treatment (ETT) Visit <10 days after the last dose of LUM/IVA (Section 9.1.2.3); and 2) subjects who interrupt LUM/IVA treatment and complete their Week 96 Visit <10 days after the last dose of LUM/IVA; it is not required for subjects who continue onto commercially-available, physician-prescribed LUM/IVA within 2 weeks (± 4 days) of completing LUM/IVA treatment at the Week 96 or ETT Visit.

The Safety Follow-up Visit is scheduled to occur 2 weeks (± 4 days) after the last dose of LUM/IVA. Safety Follow-up Visit assessments are listed in Table 3-1.

9.1.2.3 Early Termination of Treatment

Subjects who prematurely discontinue LUM/IVA treatment will be asked to complete the ETT Visit as soon as possible after the last dose of LUM/IVA. The assessments to be completed are listed in Table 3-1. If the ETT Visit occurs 10 days or later following the last dose of LUM/IVA, then the ETT Visit will replace the Safety Follow-up Visit, (i.e., the assessments performed will be those specified for the ETT Visit), and a Safety Follow-up Visit will not be required.

9.1.3 Observational Cohort

Observational Cohort assessments are listed in Table 3-2. The Observational Cohort will include the following:

- Day 1 Visit
- Long-term follow-up telephone contacts at Weeks 48 and 96

Subjects who become eligible to receive commercially-available, physician-prescribed LUM/IVA, and who choose to continue onto commercially-available LUM/IVA, must have an Early Termination Telephone Contact to terminate their participation in the study.

9.1.4 Lost to Follow-up

A subject will be considered lost to follow-up if both of the following occur:

- Subject misses 2 consecutive study visits (telephone contact and/or clinic visit) and is subsequently unable to be contacted by telephone (3 documented attempts by telephone within 2 weeks following the second missed visit)
- Subject does not respond within 2 weeks to a registered letter sent after the 3 attempted telephone contacts

9.1.5 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will be formed using the Cystic Fibrosis Foundation Data Safety Monitoring Board. The IDMC objectives and operational details will be defined in a separate document (IDMC Charter), which will be finalized before the first subject is enrolled. The IDMC will conduct regular planned reviews of study data for the purpose of safety monitoring as outlined in the IDMC Charter.

9.2 Method of Assigning Subjects to Treatment Groups

This is an open-label study. Randomization is not required. Subjects in the Treatment Cohort will be treated with LUM/IVA based on their weight and age. Subjects in the Observational Cohort will not receive LUM/IVA.

9.3 Rationale for Study Design and Study Drug Regimens

9.3.1 Study Design

Vertex has established efficacy, safety, and PK profiles for LUM/IVA in subjects 12 years of age and older, homozygous for *F508del* (Studies VX12-809-103 [Study 103] and VX12-809-104 [Study 104]). Because the underlying genetic and molecular etiology of the disease is identical between younger and older patients, and the outcome of therapy is likely to be comparable, extrapolation of efficacy from older to younger patients is appropriate and PK studies in younger patients, together with safety studies, can provide adequate information for use.[9]

Safety and PK profiles for LUM/IVA have been established in subjects 6 through 11 years of age, homozygous for *F508del* (Study VX13-809-011 [Study 011]). Study 115, a Phase 3, 2-part, open-label study, which includes a 24-week Treatment Period in Part B, is designed to obtain PK and safety information to support a proposed indication expansion of LUM/IVA in subjects aged 2 through 5 years, homozygous for *F508del*.

Study 116 is a Phase 3, open-label, multicenter study in subjects aged 2 years and older with CF, homozygous for *F508del*, who participated in Study 115B. This study, which includes a 96-week Treatment Period, is designed to evaluate the long-term safety of LUM/IVA in subjects aged 2 years and older with CF, homozygous for *F508del*.

9.3.2 Study Drug Dose and Duration

Dose of LUM/IVA

Study 115A is designed to characterize the safety and PK of LUM and IVA in subjects 2 through 5 years of age. The plasma concentration versus time data from Study 115A is intended to inform the appropriateness or necessary adjustment of planned doses for Study 115B and Study 116. As data from Study 115B become available, the doses may be modified for subjects <6 years of age in Study 116. A population PK model with allometric scaling of clearance and volume of distribution as a function of weight was used to project exposures of LUM and IVA for comparison with clinical experiences with both drugs and to select doses to be evaluated in this study population. No safety issues were identified in prior clinical or nonclinical studies that would preclude the dosing regimen proposed for Study 116.

Duration of Dosing

Subjects who receive LUM/IVA in Study 115B as well as Study 116 may receive treatment for up to approximately 2.5 years, thus providing information on the long-term safety of LUM/IVA in subjects aged 2 years and older with CF, homozygous for *F508del*.

9.3.3 Rationale for Study Assessments

The safety and PK assessments are standard parameters for clinical studies in drug development and are generally recognized as reliable, accurate, and relevant to the study of subjects with CF. OEs and spirometry assessments were added as part of safety monitoring. Assessments were added to evaluate the PD effects of LUM/IVA. The following PD assessments are standard assessments used in studies in the LUM/IVA development program: weight, stature, BMI, sweat chloride, and other events related to outcome, e.g., pulmonary exacerbations. Rationale is provided below for the following PD assessments: LCI, exocrine pancreatic function, and microbiology.

OEs: A juvenile rat toxicity study performed to support dosing of IVA in subjects <2 years of age demonstrated lens opacities in some animals.[7] Prior studies in rats and dogs of older age did not demonstrate similar findings. Given substantial differences between human and rat lens development, the finding is of unlikely relevance to humans. Periodic OEs for pediatric subjects receiving IVA or IVA in combination with a CFTR corrector are being performed to confirm this interpretation. The overall data acquired to-date does not suggest an association between IVA treatment and cataract development; however, a potential association has not been fully excluded.

Spirometry: Spirometry is included as part of standard safety monitoring. Because the quantitative assessment of pulmonary function in young children is difficult, spirometry testing will be performed only on subjects who were ≥3 years of age at screening in Study 115B. Even with this age stipulation, it is anticipated that reproducible spirometry will be obtained in a minority of the study population.

Optional LCI Assessment: LCI is a measure of ventilation inhomogeneity that is based on tidal breathing techniques that have been evaluated in patients as young as infants.[10,11] LCI correlates with FEV_1 in its ability to measure airway disease in patients with mild to moderate lung disease but can also detect lung disease at an earlier stage than spirometry.[12,13] Data from Study VX10-770-106 in subjects with CF with an FEV_1 >90% showed LCI to be a more sensitive outcome measure than FEV_1. Given the potential advantages of a more sensitive measurement during the early stages of disease progression, LCI will be used in this study. As with spirometry testing, performing LCI assessments in young children can be difficult.[14] Therefore, only subjects who were ≥3 years of age at screening in Study 115B and who consent/assent to the optional LCI Substudy will undergo the LCI assessments. LCI will be done only at selected sites that have the capability to perform these assessments.

Exocrine Pancreatic Function: The pancreas is one of the earliest and most seriously affected organs in patients with CF who are homozygous for *F508del*, a high fraction of which develop pancreatic insufficiency.

- FE-1: FE-1 is a diagnostic measure of pancreatic exocrine sufficiency, with a lack of elastase output in stool being considered indicative of CF (<200 µg/g). The increasing use of FE-1 in the clinic is a result of the ease of collecting samples for its assessment and the establishment of diagnostic cut-offs for pancreatic exocrine function.[15] FE-1 represents a feasible measure to evaluate exocrine pancreatic function during the study, with the hypothesis that rescue of pancreatic function will result in an increase in FE-1 levels.
- IRT: Trypsinogen is a protein produced by the pancreas that can be detected in the blood via the IRT assay and is used in clinical practice for neonatal screening test for CF, wherein elevated levels are associated with disease. Blood samples for IRT testing will be collected at multiple time points to evaluate potential changes in exocrine pancreatic function during the Treatment Period.

Microbiology: Microbiological endpoints, such as bacterial colony counts and selection of resistant bacterial strains, are well-established endpoints used to evaluate antimicrobial therapies in CF. Because compounds, such as IVA, that restore CFTR function may increase hydration of airway secretions and lead to a decrease in acquisition of bacteria in the CF airway, acquisition of bacteria is included as another secondary endpoint in this study. Because the majority of subjects in this study will not expectorate spontaneously, oropharyngeal swabs will be used to obtain airway cultures.

9.4 Study Restrictions

See Section 9.5 for guidance for concomitant medications.

A nonexhaustive list of study prohibitions and cautions for food and medication will be provided in the Study Reference Manual.

9.5 Medications (Treatment Cohort Only)

9.5.1 Prohibited Medications and Medications to Use With Caution

Prohibited medications and certain foods are not allowed as summarized in Table 9-1.

Table 9-1 Study Restrictions

Restricted Medication/Food	Treatment Period
Strong CYP3A inducers	None allowed
Strong CYP3A inhibitors	Use with caution

CYP: cytochrome P450
Note: The use of restricted medication in subjects with a medical need will be addressed on a case-by-case basis with the medical monitor or authorized designee.

Use of CYP3A substrates is not prohibited, but investigators need to be aware that LUM appears to be a strong inducer of CYP3A. Therefore, the efficacy of drugs extensively metabolized by CYP3A may be affected.

Use of CYP2C and 2B6 substrates is not prohibited, but investigators need to be aware that LUM has been shown in vitro to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19; inhibition of CYP2C8 and CYP2C9 has also been observed in vitro. Additionally, in vitro studies suggest that IVA may inhibit CYP2C9. Therefore, concomitant use of LUM/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 CYP3A, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 substrates with LUM and IVA and discuss their use with the medical monitor or authorized designee.

9.5.2 Prior and Concomitant Medications

It is recommended that subjects remain on a stable medication regimen for their CF from Study 115B through the Safety Follow-up Visit in Study 116. Stable medication regimen is defined as the current medication regimen for CF that subjects have been following for at least 28 days before Day 1 of Study 115B.

Subjects who are using a bronchodilator should have their LCI and spirometry assessments performed according to the guidelines provided in Section 11.6.7.

Information regarding all prior and concomitant medications, including the subject's CF medications, other medications, and herbal and naturopathic remedies administered at, or after, the Safety Follow-up Visit in Study 115B through the Safety Follow-up Visit of this study will be recorded in each subject's source documents. In addition, concomitant medication dose(s) may be collected.

9.6 Administration

LUM/IVA will be administered orally as shown in Table 9-2. Subjects in the Observational Cohort will not receive LUM/IVA.

At each study visit the LUM/IVA dose for each subject will be reassessed based on age and body weight and adjusted upward if necessary.

Table 9-2 Study Drug Administration

Population	Dose	Time	LUM/IVA (Number of Stick Packs/Tablets)
Subjects <6 years of age and weight <14 kg at enrollment[a]	LUM 100 mg/IVA 125 mg q12h[b]	AM	1 stick pack
		PM	1 stick pack
Subjects <6 years of age and weight ≥14 kg at enrollment[a]	LUM 150 mg/IVA 188 mg q12h[b]	AM	1 stick pack
		PM	1 stick pack
Subjects ≥6 years of age at enrollment[a]	LUM 200 mg/IVA 250 mg q12h	AM	2 tablets
		PM	2 tablets

IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours

[a] No downward dose adjustments will be made if a subject's weight decreases. Doses may be adjusted upward as follows:
- If a subject who is <6 years of age at enrollment enters weighing <14 kg and subsequently weighs ≥14 kg at 2 consecutive visits without becoming ≥6 years of age at these visits, the dose will be adjusted to LUM 150 mg/IVA 188 mg q12h, at the second visit where weight ≥14 kg.
- If a subject who is <6 years of age at enrollment becomes 6 years of age during the study, the dose and formulation will be adjusted to LUM 200 mg/IVA 250 mg q12h administered as tablets for oral administration, regardless of weight, at the next scheduled visit.

[b] Doses are those planned for Study 115B. Based on results from Study 115A and 115B, doses for subjects <6 years of age in Study 116 may be modified.

LUM/IVA will be administered within 30 minutes from the start of consuming fat-containing food such as a standard "CF" high-fat, high-calorie meal or snack according to the following guidelines:

1. LUM/IVA will be administered approximately q12h (± 2 hours) on each dosing occasion (e.g., if the morning dose is administered at 0800 on Day 1, the evening dose on Day 1 should be administered between 1800 and 2200 and all subsequent morning doses should be administered between 0600 and 1000).
2. The granule formulation will be dispensed by opening the stick packs containing the granules and mixing the granules with the approved foods and liquids listed in the Study Reference Manual. Each dose will be comprised of the approved food or liquids into which the granules from the stick packs are mixed. Details on preparing LUM/IVA will be provided in the Pharmacy Manual.
3. On the Day 1 Visit, all subjects will be observed for 4 hours after the first dose of LUM/IVA.
4. On days of scheduled visits (Table 3-1), with the exception of afternoon visits addressed below, the morning LUM/IVA dose will be administered at the site after predose assessments have been completed.
5. 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 LUM/IVA dose, the subject should withhold their morning dose 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 LUM/IVA 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.

6. For visits after the Day 1 Visit, subjects will be instructed to bring all used and unused LUM/IVA materials to the site; LUM/IVA will be dispensed at each visit, as appropriate.
7. At the Week 96 Visit, the LUM/IVA dose will NOT be administered. The last LUM/IVA dose will be the dose administered before the Week 96 Visit.

9.7 Dose Modification for Toxicity

Modifications of the LUM/IVA dose are prohibited. Should any unacceptable toxicity arise, individual subjects will be withdrawn from the study treatment.

9.8 Removal of Subjects

Subjects may withdraw from the study at any time at their own request or at the request of their legally appointed and authorized representative (e.g., parent or legal guardian). Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. If a subject has been withdrawn from study drug treatment, the subject will continue to be followed as noted in Sections 9.1.2.2 and 9.1.2.3, provided the subject/caregiver has not withdrawn consent.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject's parent or legal guardian. 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's parent or legal guardian return all unused investigational product(s), request that the subject return for an ETT Visit and Safety Follow-up Visit, if applicable (see Sections 9.1.2.2 and 9.1.2.3), 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.

9.9 Replacement of Subjects

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

10 STUDY DRUG INFORMATION AND MANAGEMENT

10.1 Preparation and Dispensing

LUM/IVA may be dispensed only under the supervision of the investigator or an authorized designee to the subject's legally appointed and authorized representative (e.g., parent or legal guardian) and only for administration to the study subjects.

10.2 Packaging and Labeling

Vertex will supply the LUM/IVA granules in stick packs and LUM 100-mg/IVA 125-mg tablets in child-resistant 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 as described in Section 10.4. Detailed instructions regarding the storage, handling, and dispensation of LUM/IVA will be provided in the Pharmacy Manual.

Table 10-1 Study Drug

Drug Name	Formulation/ Route	Packaging (Formulation Strength)	Storage Condition
LUM/IVA	Granules/ Oral	Supplied as 100-mg LUM/125-mg IVA granules in 1 stick pack	Store at ≤25°C (77°F) with excursions to 30°C (86°F)
LUM/IVA	Granules/ Oral	Supplied as and 150-mg LUM/188-mg IVA granules in 1 stick pack	Store at ≤25°C (77°F) with excursions to 30°C (86°F)
LUM/IVA	Fixed-dose tablet/ Oral	Supplied as 100-mg LUM/125-mg IVA tablets	Store at ≤25ºC (77ºF) with excursions to 30ºC (86ºF)

IVA: ivacaftor; LUM: lumacaftor

10.4 Drug Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of (1) study drug received; (2) study drug dispensed to the subjects; and (3) study drug returned by the subjects. Subjects will be instructed to return all used and unused materials associated with the study drug to the site. These materials will be retained at the site according to instructions provided by Vertex or its designee until inventoried by the study monitor. The study monitor will review study drug records and inventory throughout the study.

10.5 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subjects until the study monitor has performed drug accountability. At the end of the study, the study monitor will provide instructions as to the disposition of any unused investigational product. If the study monitor authorizes destruction at the study site, the investigator will ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Vertex. Destruction will be adequately documented.

10.6 Compliance

To ensure treatment compliance, the investigator or designee will supervise all study drug dosing that occurs at the site. At each visit, site personnel will review that the subject is compliant with study drug dosing and remind the subject/caregiver of study drug dosing requirements. Compliance will also be assessed by ongoing study drug count.

If a subject/caregiver demonstrates continued noncompliance of study drug dosing despite educational efforts, the investigator should contact the medical monitor to discuss discontinuation of the subject from the study treatment while remaining in the study.

10.7 Blinding and Unblinding

This will be an open-label study. However, subjects and their legally appointed and authorized representative (e.g., parent or legal guardian) should not be informed of their study-related spirometry, sweat chloride, and LCI results during the study even if the subject permanently discontinued treatment.

11 ASSESSMENTS

11.1 Timing of Assessments

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

Additional timing notes for LCI and spirometry

LCI assessments derived from N_2-multiple-breath washout (MBW) testing (Section 11.4.2) should be performed before the spirometry assessment (Section 11.6.7). MBW and spirometry testing should be performed pre-bronchodilator, which is defined as testing performed for subjects who have

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

If a subject forgets to withhold bronchodilator(s), testing should be performed as follows:

- If a subject's Day 1 testing is pre-bronchodilator, but on a subsequent visit, the subject forgets to withhold bronchodilator use, post-bronchodilator testing will be obtained for that visit only, and the visit will not be rescheduled.
- If on Day 1, the subject forgets to withhold their dose of bronchodilator, testing should be performed post-bronchodilator and all subsequent testing should be performed post-bronchodilator.
- Each test will be recorded in the source documents as pre-bronchodilator or post-bronchodilator.

11.2 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, stature, and weight. Select demographic and baseline characteristic data and medical history will be derived from the previous study.

Age, sex, race, and ethnicity will be derived from the previous study because these data are required for the normalization of spirometry values using the Global Lung Function Initiative (GLI) method (Section 11.6.7).

11.3 Pharmacokinetics

Not applicable

11.4 Pharmacodynamics

11.4.1 Sweat Chloride

Collection of sweat samples will be performed using an approved collection device. Sweat samples will be sent to a central laboratory for testing and interpretation of results. Individual sweat chloride test results will not be disclosed to the study sites. Specific instructions for collection, handling, processing, and shipping of sweat chloride samples to the central laboratory will be provided separately. The sweat chloride test will be conducted at approximately the same time as predose blood collections. At each time point, 2 samples will be collected, 1 sample from each arm (left and right).

Subjects and their parent/caregiver should not be informed of their study-related sweat chloride results during the study even if the subject prematurely discontinued treatment.

11.4.2 Lung Clearance Index

LCI assessments derived from N_2-MBW testing will be performed only on subjects who are ≥3 years of age at Study 115B screening and who consent/assent to the optional LCI Substudy in Study 115B and Study 116.

MBW should be performed "pre-bronchodilator." See Section 11.1 for pre-bronchodilator definitions and instructions if a subject forgets to withhold bronchodilator(s).

Each MBW will be performed in multiple replicates at each visit, and the final LCI value will be calculated from the technically acceptable washout replicates.

Detailed LCI procedures will be supplied in the Study Reference Manual.

Subjects and their parent/caregiver should not be informed of their study-related LCI results during the study even if the subject prematurely discontinued treatment.

11.4.3 Weight, Stature, and BMI

See Section 11.6.4.

11.4.4 Other Events Related to Outcome

11.4.4.1 Antibiotic Therapy for Sinopulmonary Sign/Symptoms

Given the absence of a consensus definition for pulmonary exacerbation in clinical studies in this population, the definition below will be applied to signs and symptoms for the analysis of pulmonary exacerbations.

Definition: New or changed treatment with oral, inhaled, or intravenous (IV) antibiotics **AND** fulfillment of 1 criterion from List A (below) or 2 criteria from List B (below), within the period 3 days before antibiotic start date through antibiotic stop date.[16]

The occurrence of any new or changed antibiotic therapy (IV, inhaled, oral) and the presence of the following signs and symptoms will be recorded in the source documents:

List A:

- Decrease in FEV_1 ≥10% change from highest value in the past 6 months before the first dose, unresponsive to albuterol (if applicable)
- Oxygen saturation <90% on room air *or* ≥5% decrease from baseline

- New lobar infiltrate(s) or atelectasis on chest x-ray
- Hemoptysis (more than streaks on more than 1 occasion in past week)

List B:

- Increased work of breathing or respiratory rate (duration ≥3 days)
- New or increased adventitial sounds on lung examination (duration ≥3 days)
- Weight loss ≥5% decrease from highest value or decrease across 1 major percentile for age in past 6 months
- Increased cough (duration ≥3 days)
- Worked harder to breathe during physical activity (duration ≥3 days)
- Increased chest congestion or change in sputum (duration ≥3 days)

It is recommended that LUM/IVA should not be interrupted during a pulmonary exacerbation unless, in the opinion of the investigator, it would be in the best interest of the subject.

The following information will be determined for protocol-defined pulmonary exacerbations:

- Number of pulmonary exacerbations
- Number of days with pulmonary exacerbations
- Time-to-first pulmonary exacerbation
- Number of pulmonary exacerbations requiring hospitalizations
- Number of days hospitalized for pulmonary exacerbations
- Time-to-first hospitalization for pulmonary exacerbation
- Number of pulmonary exacerbations requiring IV antibiotic therapy
- Number of days on IV antibiotic therapy for pulmonary exacerbations
- Time-to-first IV antibiotic therapy for pulmonary exacerbations

11.4.4.2 Hospitalization for CF

Subjects will be queried about planned and unplanned hospitalizations lasting ≥24 hours. The dates for hospitalizations and the reasons for hospitalizations will be documented.

If the hospitalization is unplanned, the procedures for safety reporting should also be followed (Section 13.1.2.3).

The following information will be determined:

- Number of planned hospitalizations for CF (i.e., prophylactic antibiotic therapy)
- Number of all unplanned hospitalizations
- Number of days of all unplanned hospitalizations
- Time-to-first unplanned hospitalization

11.4.5 Fecal Elastase-1

Stool samples for assessment of FE-1 will be collected at the study center during the study visit; however, samples may be collected by the subject's caregiver up to 24 hours before the study visit (e.g., at home) and brought to the study visit. Instructions for the collection, processing, and shipment of samples will be provided in a separate Laboratory Manual.

11.4.6 Immunoreactive Trypsinogen

Instructions for the collection, processing, and shipment of samples for assessment of IRT will be provided in a separate Laboratory Manual.

11.4.7 Microbiology Cultures

Specific instructions for the collection, processing, and shipment of samples for assessment of microbiology cultures will be provided in a separate Laboratory Manual.

11.4.8 Spirometry

See Section 11.6.7.

11.5 Efficacy

All efficacy-related assessments are listed in Section 11.4, Pharmacodynamics.

11.6 Safety

Safety evaluations will include AEs, clinical laboratory assessments (hematology, chemistry, coagulation studies, and urinalysis), clinical evaluation of vital signs, pulse oximetry, ECGs, PEs, spirometry, and OEs.

11.6.1 Adverse Events

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

11.6.2 Clinical Laboratory Assessments

The safety laboratory test panels are shown in Table 11-1. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate. Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis[a]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen	Erythrocytes:	Nitrite
Creatinine	Mean corpuscular hemoglobin	Urobilinogen
Sodium	Mean corpuscular hemoglobin concentration	Urine protein
Potassium	Mean corpuscular volume	pH
Calcium	Platelets	Urine blood
Chloride	Reticulocytes (absolute)	Specific gravity
Magnesium	Leukocytes	Urine ketones
Bicarbonate	Differential (absolute and percent):	Urine bilirubin
Inorganic phosphate	Eosinophils	Urine glucose
Total bilirubin, direct bilirubin	Basophils	
Alkaline phosphatase	Neutrophils	
Aspartate aminotransferase (=SGOT)	Lymphocytes	
Alanine aminotransferase (=SGPT)	Monocytes	
Lactate dehydrogenase	**Coagulation Studies**	
Gamma-glutamyl transferase (GGT)	Activated partial thromboplastin time	
Total protein	Prothrombin time	
Albumin	Prothrombin time International Normalized Ratio	
Creatine kinase		

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

For purposes of study conduct and data analysis, blood and urine samples will be analyzed at a central laboratory. However, at the discretion of the local investigator, samples may be analyzed at a local laboratory for management of urgent medical issues, including if a subject cannot return to the clinical study site for the mandatory liver function testing (Section 11.6.3). 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

Mandatory Liver Function Testing

Liver function testing (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], alkaline phosphatase [ALP], and total bilirubin) must be performed while subjects are receiving LUM/IVA treatment (see Table 3-1 and Section 11.6.2). These blood samples should be processed and shipped immediately per the Laboratory Manual.

Subjects with new ALT or AST elevations of ≥3 × upper limit of normal (ULN) and clinical symptoms will 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 (ALT or AST ≥3 × ULN) at the local laboratory must be reported immediately to the medical monitor AND the subject must

have the tests repeated and sent to the central laboratory as soon as possible (ideally within 48 to 72 hours).

Study Drug Interruption

LUM/IVA administration **must be interrupted** immediately, and the Vertex medical monitor or designee must be notified if any of the following criteria is met:

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

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

Resumption of Study Drug

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

Discontinuation of Study Drug

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, LUM/IVA treatment must be discontinued, after consulting 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.

11.6.4 Physical Examinations and Vital Signs

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

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

An abbreviated PE will be performed at some visits (see Table 3-1). The abbreviated PE will include an assessment of the following body systems: head/neck/thyroid, EENT, cardiovascular system, respiratory system, skin, and abdomen.

Vital signs include blood pressure (systolic and diastolic), temperature (oral), pulse rate, respiration rate, and pulse oximetry. The subject should rest for at least 5 minutes before having

vital signs measured; additional instructions will be included in a separate Study Reference Manual.

Weight and stature will be assessed and BMI will be derived. If subjects can stand unassisted and follow directions, stature should be measured as height; otherwise, stature will be measured as length. Stature and weight must be measured with shoes off and while wearing light clothing. BMI will be calculated using the following equation:

$$\text{BMI } (kg/m^2) = \text{body weight } (kg) \div \text{stature}^2 \ (m^2)$$

11.6.5 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout. Standard 12-lead ECGs will be performed with central over-reading. All sites will be provided with ECG machine(s) and associated materials by the central ECG diagnostic service.

Additional standard 12-lead ECGs will be performed at any other time if clinically indicated. The performance of all ECGs will adhere to the following guidelines:

- The subject will be instructed to rest in the supine position for at least 5 minutes, if possible, before having an ECG performed.
- The ECG will be performed before any other procedures that may affect heart rate, such as blood draws.

A printout of the ECG traces will be made for safety review by the investigator and maintained with source documentation. Clinically significant ECG abnormalities occurring during the study through the end of study participation will be recorded as AEs.

A hard copy of the ECG will be printed and signed by the investigator at the site. To ensure the safety of the subjects, the investigator or designee at the investigator site will make comparisons to the predose measurement at Day 1 (baseline). If the QTcF is increased by >45 msec from the shortest baseline QTcF or the absolute QTcF value is >500 msec for any scheduled ECG, 2 additional ECGs will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>45 msec from baseline or >500 msec), a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If the QTc value remains above the threshold value (>45 msec from baseline or >500 msec) on repeated measurement or is noted on 2 or more occasions with no identified alternative etiology for the increased QTc, then discontinuation from LUM/IVA treatment may be required after discussion with the Vertex medical monitor or designee. Subjects who have treatment discontinued for increased QTcF should have their QTcF monitored closely until it normalizes or returns to baseline.

ECG data will be transmitted via modem to the central ECG diagnostic service. A cardiologist at the central ECG diagnostic service will review each ECG to confirm if intervals were calculated correctly and to provide an interpretation including a suggested clinical significance, as applicable. A report containing this information will be provided to the site for review and signature by the investigator. This report will be filed with the machine ECG report for each time point in the subject's source documents. The values reported by the central ECG diagnostic service will be used for data analysis.

11.6.6 Ophthalmologic Examination

The OE includes

- measurement of best corrected distance visual acuity of each eye; and
- pharmacologically dilated examination of the lens with a slit lamp.

OEs must be conducted by a licensed ophthalmologist. Subjects with documentation of bilateral lens removal do not need the OE.

If a cataract or lens opacity is identified and determined to be clinically significant by a licensed ophthalmologist at the Day 1 OE, the subject/caregiver will be notified. After discussion with the site principal investigator, and in collaboration with the Vertex medical monitor, the subject/caregiver may elect to participate or not to participate in the study. If the subject continues in the study, more frequent ophthalmologic monitoring should be considered.

If a cataract or lens opacity is identified and determined to be clinically significant by a licensed ophthalmologist after dosing, the subject/caregiver will be notified. After discussion with the site principal investigator and in collaboration with the Vertex medical monitor, the subject/caregiver may elect to continue or discontinue LUM/IVA. If the subject discontinues LUM/IVA, the subject will be asked to remain in the study and complete the study assessments as noted in Section 9.1.2.3. If the subject continues, more frequent ophthalmologic monitoring should be considered.

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

11.6.7 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines.[17] Spirometry will be performed only on subjects who are ≥3 years of age at screening of Study 115B.

Spirometry should be performed "pre-bronchodilator." See Section 11.1 for pre-bronchodilator definitions and instructions if a subject forgets to withhold bronchodilator(s).

The parameters listed below will be normalized using the standards of GLI.[18]

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

The central spirometry service will provide all sites with spirometers and associated materials to be used for all study assessments. Spirometry data will be transmitted to a centralized spirometry service for quality review.

Subjects and their parent/caregiver should not be informed of their study-related spirometry results during the study even if the subject prematurely discontinued treatment.

11.6.8 Contraception and Pregnancy

Not applicable

12 STATISTICAL AND ANALYTICAL PLANS

Analysis of long-term safety and PD will be performed by Vertex or its designee, and will be presented in the corresponding statistical analysis plan (SAP).

12.1 Sample Size and Power

No formal sample size calculations have been performed.

This is a long-term extension that plans to enroll subjects rolled over from Study 115B. Approximately 56 subjects are potentially eligible to be enrolled in this rollover study. Assuming a 10% dropout rate in Study 115B, 50 subjects are expected to enroll in this study.

12.2 Analysis Sets

All Subjects Set is defined as all subjects who have signed informed consent (and assent, if applicable) and enrolled or dosed in Study 115B.

116 All Subjects Set is defined as all subjects who have signed informed consent (and assent, if applicable) and enrolled or dosed in the Study 116 Treatment Cohort.

Safety Sets

Safety Set: The Safety Set will include all subjects who received at least 1 dose of study drug in Study 115B.

116 Safety Set: The 116 Safety Set will include all subjects dosed in Study 115B who are exposed to any amount of study drug in the Study 116 Treatment Cohort.

Efficacy Sets

Full Analysis Set (FAS): The FAS will include all subjects who were enrolled and exposed to any amount of study drug in Study 115B.

Other Analysis Sets

LCI Substudy Set will include all subjects who have signed informed consent (and assent, if applicable) to the optional LCI Substudy and enrolled and dosed in Study 115B.

116 LCI Substudy Set is a subset of LCI Substudy Set, who are enrolled and exposed to any amount of study drug in the Study 116 Treatment Cohort.

Analysis Period

Cumulative Study Period starts from the first dose of study drug in the previous study to the last day in Study 116, regardless of 1) the planned 2-week Washout Period in Study 115B; or 2) the rollover gap between Study 115B and Study 116. For subjects not enrolled in Study 116, the Cumulative Study Period will start from the first dose of study drug in the previous study to the last day in the previous study.

Treatment-emergent Period for the Cumulative Study Period

The Treatment-emergent Period for the Cumulative Study Period is the period on or after the first dose of study drug in the previous study to 14 days (inclusive) after the last dose of study drug in Study 116 or up to the last day in Study 116, whichever occurs first. For subjects not enrolled in Study 116, the Treatment-emergent Period for the Cumulative Study Period will be

the period on or after the first dose of study drug in the previous study to 14 days (inclusive) after the last dose of the previous study, or last date of the previous study, whichever occurs first.

Other specific periods may be defined in the SAP and used for any targeted analysis as deemed necessary.

12.3 Statistical Analysis

Statistical Analysis System Version 9.2 or higher will be used to generate all statistical outputs (tables, figures, listings, and data sets).

Statistical analysis and presentation details will be provided in the SAP that will be finalized before the data cut/lock.

12.3.1 General Considerations

For the Treatment Cohort, all individual subject data will be presented in data listings based on All Subjects Set.

For the Observational Cohort, listings will be provided only for disposition, demographics, and serious adverse events (SAEs). Listings will be provided based on all subjects enrolled in the Observational Cohort.

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

Categorical variables will be summarized using counts and percentages.

Baseline value:

- Baseline of Cumulative Study Period:

  The baseline value is defined as the most recent non-missing measurement before intake of the first dose of study drug in Study 115B.

  - For LCI-related parameters, the values at each visit will be calculated from the technically acceptable washout replicates. The baseline of LCI will be the most recent non-missing value calculated from the technically acceptable replicates before the initial administration of study drug of Study 115B.
  - For sweat chloride, the values at each visit will be based on the averaged measurements from left and right arms. The baseline will be defined as the average of the values at screening and the pretreatment measurement on Day 1 of Study 115B. If only 1 pre-first dose measurement of sweat chloride is available, that measurement will be considered the baseline.

Change (Absolute Change) from baseline will be calculated as post baseline value − baseline value.

Relative change from baseline will be calculated and presented in percentage as 100 × (post baseline value − baseline value)/baseline value.

12.3.2 Background Characteristics

Treatment Cohort

Summary will be provided overall and by the initial dosing groups (LUM 100 mg/ IVA 125 mg q12h; LUM 150 mg/IVA 188 mg q12h) as supplementary information.

12.3.2.1 Subject Disposition

Numbers of the following categories for the population will be provided:

- All Subjects Set
- 116 All Subjects Set
- Safety Set
- 116 Safety Set
- FAS
- LCI Substudy Set
- 116 LCI Substudy Set

Treatment Cohort

Subject disposition categories will be summarized for Study 116 based on the 116 Safety Set. Numbers and percentages of subjects will be provided with the number in the 116 Safety Set as denominator. The number of subjects enrolled but never dosed in Study 116 will be provided without a percentage.

- Enrolled but never dosed (only showing number of subjects)
- Completed treatment
- Prematurely discontinued treatment and the reasons for discontinuations
- Completed study (any subject who has completed the Safety Follow-up Visit)
- Prematurely discontinued the study and the reasons for discontinuations
- Last scheduled on treatment visit completed for subjects who discontinued treatment

A similar disposition table will be provided based on the 116 LCI Substudy Set.

Observational Cohort

Subject disposition will be listed based on all subjects enrolled in the Study 116 Observational Cohort.

12.3.2.2 Demographics and Baseline Characteristics

Treatment Cohort

Demographics, baseline characteristics, and medical history will be summarized with respect to the start of Study 115B overall and by initial dosing of Study 115B separately for the 116 Safety Set, and the 116 LCI Substudy Set.

Important protocol deviations/violations will be provided as a subject data listing only based on the 116 All Subjects Set. The rules used to define the important protocol deviations/violations will be provided in the SAP.

Observational Cohort

Demographics and baseline characteristics will be listed with respect to the start of Study 115B overall using all subjects enrolled in the Observational Cohort.

12.3.2.3 Prior and Concomitant Medications

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

- **Prior medication:** medication continued or newly received before initial dosing of study drug in the previous study.
- **Post-treatment medication**: any medication continued or newly received after the end of the Treatment-emergent Period of the Cumulative Study Period
- **Concomitant medication**: medication continued or newly received during the Treatment-emergent Period of the Cumulative Study Period.

A given medication can be classified as a prior medication, concomitant medication, or a post-treatment medication; both concomitant and post-treatment; both prior and concomitant; prior, concomitant, and post-treatment. Incidence of prior medication will be summarized based on the 116 Safety Set by 1) preferred name; 2) anatomic class (ATC) level 1; ATC level 2; and preferred name.

Incidence of concomitant medication as well as the exposure adjusted number of concomitant medication will be summarized based on the Safety Set for the Cumulative Study Period by 1) preferred name; 2) ATC level 1; ATC level 2; and preferred name.

All medications in the Cumulative Study Period will be listed for each subject.

12.3.2.4 Study Drug Exposure and Compliance

Study Drug Exposure

Duration of study drug exposure is defined as follows: last dose date of the Cumulative Study Period − first dose date of the Cumulative Study Period + 1 day, regardless of any dose interruptions.

Duration of study drug exposure as well as number of sticks administered defined as (total number of sticks dispensed) − (total number of sticks returned) will be summarized descriptively overall based on Safety Set for the Cumulative Study Period. Additionally, the total duration of treatment exposure, defined as the sum of the subject's duration of treatment exposure and expressed in subject-years, will be provided. Duration of exposure will also be summarized as a categorical variable.

Study Drug Compliance

Study drug compliance will be calculated as follows: 100 × (1 − [total number of days of study drug interruption in the Cumulative Study Period] / [duration of study drug exposure in the Cumulative Study Period). The total number of days of study drug interruption is defined as the

sum of (number of days of each study drug interruption in the Cumulative Study Period), where number of days of each study drug interruption is defined as the interruption end date − the corresponding interruption start date + 1.

Treatment compliance percentages will be summarized descriptively (number, mean, SD, median, minimum, and maximum) overall based on Safety Set for the Cumulative Study Period. The number and percentage of subjects whose compliance is <80% or ≥80% will be summarized.

12.3.3 Pharmacodynamic Analysis

12.3.3.1 Analysis of Primary Variables

Not applicable

12.3.3.2 Analysis of Secondary Pharmacodynamic Endpoints

12.3.3.2.1 Absolute Change from Baseline: Sweat Chloride, BMI, BMI-for-Age Z-score, Weight, Weight-for-Age Z-score, Stature, Stature-for-Age Z-score, and LCI

For the secondary endpoint of sweat chloride, raw and absolute change from the Cumulative Study Baseline in sweat chloride at each visit in the Cumulative Study Period (including all measurements from Study 115B and Study 116, including the Safety Follow-up Visit of Study 116, both on-treatment measurements and measurements after treatment discontinuation), will be summarized based on FAS. Descriptive statistics including number of subjects, mean, SD, SE, median, minimum, and maximum, along with the 95% CI and within-group *P* value based on Normal approximation, will be provided for the absolute change from the Cumulative Study Baseline. The mean (95% CI) of the absolute change from baseline will be plotted. The following secondary endpoints will be summarized similarly as described above for sweat chloride based on FAS:

- Absolute change from Cumulative Study Baseline in BMI and BMI-for-age z-score
- Absolute change from Cumulative Study Baseline in weight and weight-for-age z-score
- Absolute change from Cumulative Study Baseline in stature and stature-for-age z-score
- Absolute change from Cumulative Study Baseline in $LCI_{2.5}$
- Absolute change from Cumulative Study Baseline in $LCI_{5.0}$

12.3.3.2.2 Analysis of Pulmonary Exacerbation-related Other Secondary Pharmacodynamic Variables

- **Time-to-first pulmonary exacerbation:** Time-to-first pulmonary exacerbation, defined as days from study drug initiation in the previous study to first pulmonary exacerbation, will be analyzed using Kaplan-Meier method based on Safety Set for the Cumulative Study Period. Cumulative incidence of pulmonary exacerbation will be summarized and plotted. Subjects without an exacerbation will be considered censored at the end date of the Cumulative Study Period.

- **Number of pulmonary exacerbations:** The number of pulmonary exacerbations starting during the Cumulative Study Period (including both on-treatment events and events after treatment discontinuation), normalized by the time spent in the Cumulative Study Period (last date in the Cumulative Study Period – first date in the Cumulative Study Period + 1), will be summarized for the Cumulative Study Period.
- **Number of CF-related hospitalizations through last visit:** For number of CF-related hospitalizations occurring during the Cumulative Study Period, the analysis will be similar to the analysis of number of pulmonary exacerbations.

12.3.3.2.3 Absolute Change in FE-1 Levels From Baseline

Raw values and absolute change from Cumulative Study Baseline in FE-1 levels at each visit in the Cumulative Study Period will be summarized descriptively based on FAS, similar to sweat chloride.

12.3.3.2.4 Absolute Change in Serum Levels of IRT From Baseline

Raw values and absolute change from Cumulative Study Baseline in IRT at each visit in the Cumulative Study Period will be summarized descriptively based on FAS, similar to sweat chloride.

12.3.3.2.5 Change in Microbiology from Baseline

Raw values and absolute change from Cumulative Study Baseline in microbiology at each visit in the Cumulative Study Period will be summarized descriptively based on FAS, similar to sweat chloride. Percentage of subjects with cultures positive at each visit in the Cumulative Study Period will be summarized descriptively based on the FAS for each possibly-detected organism.

Additional analysis may be added in the SAP, if any.

[redacted]

12.3.4 Safety Analysis

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

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis)
- ECGs (standard 12-lead)
- Vital signs
- Pulse oximetry
- OEs
- Spirometry (subjects ≥3 years age at screening in Study 115B)

The safety analysis will be based on the Safety Set. All listings will be provided based on the All Subjects Set.

12.3.4.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs, or post-treatment AEs.

- **Pretreatment AEs:** AEs occurred before initial dosing of study drug in the previous study.
- **TEAE:** any AE that increased in severity or that was newly developed during the Treatment-emergent Period of the Cumulative Study Period.
- **Post-treatment TEAE:** any AE that increased in severity or that was newly developed after the end of the Treatment-emergent Period of the Cumulative Study Period.

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

All TEAE summaries will be described, using number and percentages of subjects, as well as number of events per 100 patient-years (number of events adjusted for the total duration of exposure) for the Cumulative Study Period. An overview of the TEAE profile will be provided, including total number of TEAEs, with number and percentage of subjects as well as number of events per 100 patient-years for the following categories: (1) all TEAEs; (2) Grade 3/4 TEAEs; (3) TEAEs by relationship; (4) TEAEs by maximum severity; (5) TEAEs leading to treatment interruption; (6) TEAEs leading to treatment discontinuation; (7) serious TEAEs; (8) related serious TEAEs; and (9) TEAEs leading to death.

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

- All TEAEs
- Grade 3/4 TEAEs
- TEAEs by relationship
- TEAEs by maximal severity
- TEAEs leading to treatment interruption
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- Related serious TEAEs
- TEAEs leading to death
- Frequently reported TEAEs

Summaries will be presented by MedDRA system organ class (SOC) and preferred term (PT) using frequency counts and percentages and number of events per 100 patient-years (i.e., number and percentage of subjects with an event as well as exposure-adjusted number of events). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once, only the maximum severity level will be presented in the severity summaries, and the worst/highest relationship

level in the relationship summaries. In addition, listings containing individual subject data for all TEAEs leading to treatment interruption, TEAEs leading to treatment discontinuation, deaths, and SAEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

A listing of SAEs for the Observational Cohort will be provided based on all subjects enrolled in the Observational Cohort.

12.3.4.2 Clinical Laboratory Assessments

For the laboratory measurements, the raw values and change from Cumulative Study Baseline of the continuous hematology and chemistry results will be summarized in SI units at each visit in the Cumulative Study Period.

For hematology and chemistry, the number and percentage of subjects with abnormal low (<lower limit of normal [LLN]) value and with abnormal high (>ULN) value at each scheduled time point in the Cumulative Study Period will be summarized.

The number and percentage of subjects with at least 1 categorical change during the Treatment-emergent Period of the Cumulative Study Period will be provided.

The categorical criteria will be provided in the SAP.

Results of urinalysis will be listed in individual subject data listings only. In addition, a listing containing individual subject hematology, chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

12.3.4.3 Electrocardiogram

For the ECG measurements, a summary of raw values and change from Cumulative Study Baseline values will be provided at each scheduled time point of the Cumulative Study Period, for the following standard digital ECG measurements: PR, QT, and QT corrected for HR (QTc) intervals (Fridericia's correction [$QTcF = QT/RR^{1/3}$], QRS duration, and HR. In addition, the mean value at each time point will be plotted for QTcF.

The number and percentage of subjects with at least 1 categorical change during the Treatment-emergent Period of the Cumulative Study Period will be summarized.

The categorical criteria will be provided in the SAP.

The number and percentage of subjects with shift changes from Cumulative Study Baseline (normal/missing, not clinically significant, and potentially clinically significant according to overall ECG evaluation) to the worst ECG evaluation during the Treatment-emergent Period of the Cumulative Study Period will be summarized.

12.3.4.4 Vital Signs

For the vital signs measurements, the raw values and change from Cumulative Study Baseline values will be summarized at each scheduled time point of the Cumulative Study Period: systolic and diastolic blood pressure (mm Hg), body temperature (^{o}C), pulse rate (beats per minute), and respiratory rate (breaths per minute).

The number and percentage of subjects with at least 1 categorical change during the Treatment-emergent Period of the Cumulative Study Period will be summarized.

The categorical criteria will be provided in the SAP.

12.3.4.5 Pulse Oximetry

For the pulse oximetry measurements, a summary of raw values and change from Cumulative Study Baseline values will be provided at each scheduled time point of the Cumulative Study Period for the percent of oxygen saturation by pulse oximetry.

The number and percentage of subjects with shift changes from Cumulative Study Baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the Treatment-emergent Period of the Cumulative Study Period will be summarized.

12.3.4.6 Ophthalmological Examinations

OE findings will be presented as a data listing.

12.3.4.7 Spirometry

Spirometry data will be summarized descriptively at each visit based on the Safety Set for subjects who are ≥3 years of age at screening in Study 115B. The raw values and absolute change/relative change from Cumulative Study baseline values will be summarized at each scheduled time point of the Cumulative Study Period.

12.3.4.8 Physical Examination

PE findings will be presented as a data listing only.

12.3.4.9 Other Safety Analysis

Not applicable

12.3.5 Interim and IDMC Analyses

12.3.5.1 Interim Analysis

No interim analysis is planned but interim analyses may take place at any time during the study if warranted by the ongoing data, and/or deemed necessary by the internal Vertex team.

12.3.5.2 IDMC Analysis

Details of the IDMC (Section 9.1.5) analysis will be provided in the IDMC Analysis Plan.

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

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

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

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

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

13.1.1.3 Documentation of Adverse Events

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

- Withdrawal of consent
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, the earliest of
  - 18 days after the last dose of study drug, or
  - the ETT Visit, if that visit is 10 days or later following the last dose of study drug (see Section 9.1.2.3)

NOTE: Only SAEs will be collected for the Observational Cohort.

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

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

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

13.1.1.4 Adverse Event Severity

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

Table 13-1 Grading of AE Severity

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

13.1.1.5 Adverse Event Causality

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

Table 13-2 Classifications for AE Causality

Classification	Definition
Related	There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event reappeared on re-exposure to the investigational study drug.
Possibly related	There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
Unlikely related	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
Not related	The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the study subject's medical 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 signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure will not be considered to indicate an SAE, unless an AE caused the hospitalization or procedure to be rescheduled sooner or to be prolonged relative to what was planned. In addition, hospitalizations clearly not associated with an AE (e.g., social hospitalization for purposes of respite care) will not be considered to indicate an SAE.

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

13.1.2.2 Documentation of Serious Adverse Events

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

SAEs will be recorded on the Vertex Organized Safety Information Collection Form (hereafter referred to as the "SAE Form") using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for relationship to the investigational study drug(s) and possible etiologies. On the SAE Form, relationship to study drug(s) will be assessed only as related (includes possibly related) or not related (includes unlikely related), and

severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report to Vertex the outcome of the event using the SAE Form.

13.1.2.3 Reporting Serious Adverse Events

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

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

Contact Telephone: [redacted]

13.1.2.4 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to central 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 and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

13.2.3 Investigator Compliance

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

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

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

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

13.2.6 Record Retention

The investigator will maintain all study records according to ICH GCP guidelines and/or applicable local regulatory requirement(s), whichever is longest, as described in the Clinical

Trial Agreement. If the investigator withdraws from the responsibility of keeping the study records, custody will be transferred to a person willing to accept the responsibility and Vertex will be notified.

13.2.7 Study Termination

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

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

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the FDA or other regulatory authority

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

13.3 Data Quality Assurance

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

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

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

13.4 Monitoring

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

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

13.5 Electronic Data Capture

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

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

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

The audit trail entry will show the user's identification information and the date and time of any correction. The investigator will provide formal approval of all the information in the CRFs, including any changes made to the CRFs, to endorse the final submitted data for the subjects for whom the investigator is responsible.

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

13.6 Publications and Clinical Study Report

13.6.2 Clinical Study Report

A clinical study report, written in accordance with the ICH E3 Guideline, will be submitted in accordance with local regulations.

14 REFERENCE

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX16-809-116	Version #: 1.1	Version Date: 10 October 2016
Study Title: A Phase 3, Rollover Study to Evaluate the Safety of Long-term Treatment With Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation		

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

[redacted]

15.2 Investigator Signature Page

Protocol #: VX16-809-116	Version #: 1.1	Version Date: 10 October 2016
Study Title: A Phase 3, Rollover Study to Evaluate the Safety of Long-term Treatment With Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation		

I have read Protocol VX16-809-116, Version 1.1, 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