1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3, 2-Part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

Vertex Study Number: VX15-809-115

[redacted]

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Vertex Pharmaceuticals Incorporated
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2 PROTOCOL SYNOPSIS

Title A Phase 3, 2-Part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

Brief Title Safety and Pharmacokinetic Study of Lumacaftor/Ivacaftor in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for *F508del*

Clinical Phase and Clinical Study Type Phase 3 safety and pharmacokinetics (PK)

Objectives

Primary Objectives

Part A

To evaluate the PK of lumacaftor (LUM) and ivacaftor (IVA) and their respective metabolites in subjects aged 2 through 5 years with cystic fibrosis (CF), homozygous for *F508del*

Part B

To evaluate the safety of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for *F508del*

Secondary Objectives

Part A

To evaluate the safety of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for *F508del*

Part B

- To evaluate the pharmacodynamics (PD) of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for *F508del*
- To evaluate the off-drug PD response after the Washout Period
- To evaluate the PK of LUM and IVA and their respective metabolites in subjects aged 2 through 5 years with CF, homozygous for *F508del*

Endpoints

Primary Endpoints

Part A

PK parameters of LUM and IVA

Part B

Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis), standard 12-lead electrocardiograms (ECGs), vital signs, pulse oximetry, ophthalmological examinations, and spirometry

Secondary Endpoints

Part A

- PK parameters of the metabolites of LUM and IVA
- Safety and tolerability assessments based on AEs, clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, and spirometry

Part B

- Absolute change from baseline in sweat chloride at Week 24
- Absolute change from baseline in body mass index (BMI) and BMI-for-age z-score at Week 24
- Absolute change from baseline in weight and weight-for-age z-score at Week 24
- Absolute change from baseline in stature and stature-for-age z-score at Week 24
- Time-to-first pulmonary exacerbation through Week 24
- Number of pulmonary exacerbations through Week 24
- Number of CF-related hospitalizations through Week 24
- Absolute change in fecal elastase-1 (FE-1) levels from baseline at Week 24
- Absolute change in serum levels of immunoreactive trypsinogen (IRT) from baseline through Week 24
- Change in microbiology cultures from baseline at Week 24
- Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at Week 24
- Absolute change in sweat chloride from Week 24 at Week 26
- Acceptability/palatability of LUM/IVA granules at Day 1
- Absolute change from baseline in lung clearance index $(LCI)_{2.5}$ at Week 24
- Absolute change from baseline in $LCI_{5.0}$ at Week 24
- PK parameters of LUM, IVA, and their respective metabolites

Number of Subjects

Part A

Approximately 12 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 10 subjects should complete Part A. Approximately half of the subjects should complete the study in each of the following weight groups: <14 kg and ≥14 kg at screening. Subjects who participate in Part A may participate in Part B.

A review of safety, tolerability, and available PK data will be completed by an internal team at Vertex Pharmaceuticals Incorporated (Vertex) after Part A to determine the dose(s) to be evaluated in Part B. Additional subjects or treatment cohorts may be enrolled, if data from the initial, planned, 12 subjects are inadequate to make a determination of the dose(s) to be evaluated in Part B.

Part B

Approximately 56 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 50 subjects should complete Part B; at least 10 subjects must be <3 years of age. Subjects should be ≥3 years of age for enrollment in the optional LCI Substudy at a subset of sites. Additional subjects may be enrolled at the sponsor's discretion to achieve up to 30 subjects in the LCI Substudy.

Study Population

Part A and Part B

Male and female subjects 2 through 5 years of age (inclusive) with CF who are homozygous for the *F508del-CF transmembrane conductance regulator (CFTR)* mutation

Investigational Drug

Active substance: LUM and 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

Doses Investigated and Dose Adjustment in Part A:

- LUM 100 mg/IVA 125 mg q12h for subjects weighing <14 kg at screening
- LUM 150 mg/IVA 188 mg q12h for subjects weighing ≥14 kg at screening

Doses are based on the subject's weight at screening of Part A.
No dose adjustments will be made across the duration of treatment.

Doses Investigated and Dose Adjustment in Part B:

A review of safety, tolerability, and available PK data will be completed by an internal Vertex team after Part A to determine the dose(s) chosen for evaluation in Part B. Two doses will be evaluated based on weight at screening of Part B:

- LUM 100 mg/IVA 125 mg q12h for subjects weighing <14 kg at screening
- LUM 150 mg/IVA 188 mg q12h for subjects weighing ≥14 kg at screening

No dose adjustments will be made across the duration of treatment.

Note: doses listed above are the planned doses for Part B. Depending on the results from Part A, a single dose from Part A may be selected for all subjects or a previously unspecified dose or doses may be selected for Part B.

Study Duration

Part A

The total duration is approximately 53 days (up to 28 days for the Screening Period, 15 days for the Treatment Period, and 10 days for the Safety Follow-up Period).

Part B

The total duration is approximately 30 weeks (up to 28 days for the Screening Period, 24 weeks for the Treatment Period, and 2 weeks for the Safety Follow-up Period).

Study Design

Part A

Part A includes the following:

- Screening Period (Day -28 through Day -1)
- Treatment Period (Day 1 through Day 15 ± 2 days; the last dose of LUM/IVA in Part A is the morning dose on Day 15)
- Safety Follow-up Visit (10 ± 3 days after the last dose of LUM/IVA)

A review of safety, tolerability, and available PK data will be completed by an internal Vertex team after Part A to confirm or adjust the dose(s) chosen for Part B. Pending PK data from Part A, the dose planned for Part B may be adjusted. Additional subjects or treatment cohorts may be enrolled, if data from the initial, planned, 12 subjects are inadequate to make a determination of the dose(s) to be evaluated in Part B.

Part B

Part B includes the following:

- Screening Period (Day -28 through Day -1)
- Treatment Period (Day 1 through Week 24 ± 5 days; the last dose of LUM/IVA in Part B is the evening dose before the Week 24 visit.)

- Washout Period (Week 24 to Week 26 ± 4 days)
- Safety Follow-up Visit (Week 26 [2 weeks ± 4 days after the last dose of LUM/IVA])

Subjects who permanently discontinue LUM/IVA treatment will be asked to remain in the study and to complete the study assessments from the time of LUM/IVA treatment discontinuation through the Week 24 Visit, or Safety Follow-up Visit as applicable, in Part B.

Assessments

Safety (Part A and Part B)

AEs, clinical laboratory values (serum chemistry, hematology, coagulation, and urinalysis), ECGs, vital signs, pulse oximetry, physical examinations, spirometry (subjects ≥3 years of age at screening of Part A or Part B), and ophthalmologic examinations (Part B)

Pharmacokinetic (Part A and Part B)

PK parameters of LUM, IVA, and their respective metabolites

Pharmacodynamic (Part B only)

Sweat chloride test, BMI/BMI-for-age z-score, weight/weight-for-age z-score, stature/stature-for-age z-score, spirometry (subjects ≥3 years of age at screening of Part B), LCI (subjects ≥3 years of age at screening of Part B who consent/assent to the optional LCI Substudy), pulmonary exacerbations, CF-related hospitalizations, FE-1, IRT, qualitative microbiology cultures, and acceptability/palatability of LUM/IVA granules

Statistical Analyses

Part A

No formal sample size calculations have been performed. The number of subjects participating in each weight group is common in early clinical pharmacology studies and is considered sufficient to achieve the PK objectives of Part A.

Details of the analysis will be provided in the Part A statistical analysis plan.

Part B

No formal sample size calculations have been performed. The number of subjects in Part B is deemed adequate to meet the primary safety objective.

Approximately 56 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 50 subjects will complete Part B. Given a total sample size of 50 subjects (completers), there is a 92.3% chance of observing AEs in at least 1 subject if the true incidence rate is 5%, and a 99.5% chance of observing AEs in at least 1 subject if the true incidence rate is 10%.

For primary safety analyses, overall summary statistics will be provided for treatment-emergent adverse events (TEAEs), clinical laboratory assessments (serum chemistry, hematology, and coagulation studies), standard 12-lead ECGs, vital signs, pulse oximetry, and spirometry (subjects ≥3 years of age at screening). If weight-based dosing is used for Part B, summary by dosing groups will also be provided as supplementary information.

Details of the analysis will be provided in the Part B statistical analysis plan.

IDMC Reviews

An independent data monitoring committee (IDMC) is planned for Part B only. Before the start of Part B, the IDMC may be consulted at the discretion of the sponsor. The IDMC objectives and operational details will be defined in a separate document (the IDMC Charter), which will be finalized before the first subject is enrolled in Part B. 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

Schedules of Assessments are shown in the following tables:

Table 3-1 for the Part A Screening Period

Table 3-2 for the Part A Treatment Period and Safety Follow-up Visit

Table 3-3 for the Part B Screening Period

Table 3-4 for the Part B Treatment Period and Safety Follow-up Visit

Table 3-1 Study VX15-809-115: Part A Screening

Assessment	Screening Visit Day -28 through Day -1
Informed consent/assent	X
Demographics	X
Medical and ophthalmological history	X
Stature, weight, and vital signs[a,b]	X
Pulse oximetry[b]	X
Ophthalmologic examination[c]	X
Full physical examination	X
Standard 12-lead ECG[d]	X
Spirometry[e]	X
CFTR genotype[f]	X
Serum chemistry[g]	X
Hematology[g]	X
Coagulation studies[g]	X
Urinalysis[g]	X
Medications review[h]	Continuous from signing of ICF through Safety Follow-up Visit
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit

BMI: body mass index; *CFTR*: *cystic fibrosis transmembrane conductance regulator* gene;
ECG: electrocardiogram; ICF: informed consent form

[a] If children 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. Refer to Section 11.4.3 for details.

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

[c] An ophthalmologic examination will be conducted by a licensed ophthalmologist. The examination does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the Screening Visit. Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination. Refer to Section 11.6.6 for details.

[d] 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. Refer to Section 11.6.5 for details.

[e] Spirometry (subjects ≥3 years of age at screening only) may be performed pre- or post-bronchodilator. Refer to Section 11.6.7 for details.

[f] All subjects will be tested to assess *CFTR* genotype, regardless of availability of a previous CFTR genotype laboratory report. Refer to Section 11.6.2 for details.

[g] Refer to Section 11.6.2 for details.

[h] Refer to Section 9.4.2 for details.

Table 3-2 Study VX15-809-115: Part A Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Day 1	Day 3 (± 1 Day)	Day 8 (± 1 Day)	Day 15 (± 2 Days)	Safety Follow-up Visit 10 (± 3) Days After the Last Dose of Study Drug
Clinic visit	X		X	X	X
Telephone contact[b]		X			
Safety Assessments					
Stature and weight[c]	X			X	X
Vital signs[d]	X		X	X	X
Pulse oximetry[d]	X		X	X	X
Full physical examination[e]	X			X	X
Standard 12-lead ECG[f]	X[g]			X[g]	X
Spirometry[h]	X		X	X	X
Serum chemistry[i]	X		X[j] (LFT only)	X	X
Hematology[i]	X			X	X
Coagulation studies[i]	X			X	X
Urinalysis[i]	X			X	X

[a] All assessments will be performed before LUM/IVA dosing unless noted otherwise (Section 11.1). When repeats of an assessment are required postdose at a given visit, the assessment will be collected only once if LUM/IVA is not administered on the day of the visit (i.e., LUM/IVA interruption or permanent LUM/IVA discontinuation).

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

[c] If children 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. Refer to Section 11.4.3 for details.

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

[e] Symptom-directed physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator. Refer to Section 11.6.4 for details.

[f] 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. Refer to Section 11.6.5 for details.

[g] Standard 12-lead ECGs will be performed at the following times: at the Day 1 and Day 15 Visits before the morning dose of LUM/IVA, and at 1.5, 3, 4, and 6 hours after the morning dose of LUM/IVA. Predose ECGs on Day 1 will be performed in triplicate. A window of ± 15 minutes will be allowed around the nominal times for all postdose ECG assessments.

[h] Spirometry (subjects ≥3 years of age at screening only) should be performed pre-bronchodilator. On Day 1, spirometry will be performed before the morning dose and 4 hours (± 30 minutes) after the morning dose of LUM/IVA. On Day 8 and Day 15, spirometry will be performed before the morning dose of LUM/IVA. Refer to Section 11.6.7 for details.

[i] Refer to Section 11.6.2 for details.

[j] Liver function testing (ALT, AST, GGT, ALP, and total bilirubin) will be performed at the Day 8 Visit. Refer to Section 11.6.2 for details.

Table 3-2 Study VX15-809-115: Part A Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Day 1	Day 3 (± 1 Day)	Day 8 (± 1 Day)	Day 15 (± 2 Days)	Safety Follow-up Visit 10 (± 3) Days After the Last Dose of Study Drug
Observation 4 hours after the first dose	X				
Medications, treatments, and procedures review[k]	Continuous from signing of ICF through Safety Follow-up Visit				
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit				
PK Assessments					
PK sampling	X[l]		X[m]	X[n]	
Study Drug Administration					
LUM/IVA dosing[o]	**LUM/IVA q12h Day 1 through Day 15 (morning dose only on Day 15)**				

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CF: cystic fibrosis; ECG: electrocardiogram; GGT: gamma glutamyl transpeptidase; ICF: informed consent form; IVA: ivacaftor; LFT: liver function testing; LUM: lumacaftor; PK: pharmacokinetic; q12h: every 12 hours

k Refer to Section 9.4.2 for details.
l On Day 1, a PK blood sample will be collected at 3 to 4 hours after the morning dose of LUM/IVA. Refer to Section 11.3.1 for details.
m On Day 8, PK blood samples will be collected predose (within 60 minutes before the morning dose). Refer to Section 11.3.1 for details.
n On Day 15, a PK blood samples will be collected predose (within 60 minutes before the morning dose), and 2 hours (± 15 minutes) and 3 to 4 hours after the morning dose of LUM/IVA. Refer to Section 11.3.1 for details.
o LUM/IVA will be administered q12h (± 1 hour), approximately 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 guidelines in Section 10.2.1. The morning dose on Day 15 is the last dose of LUM/IVA.

Table 3-3 Study VX15-809-115: Part B Screening

Assessment	Screening Visit Day -28 through Day -1
Informed consent/assent	X
Demographics	X
Medical and ophthalmological history	X
Stature, weight, and vital signs[a,b]	X
Pulse oximetry[b]	X
Ophthalmologic examination[c]	X
Full physical examination	X
Standard 12-lead ECG[d]	X
CFTR genotype[e]	X
Serum chemistry[f]	X
Hematology[f]	X
Coagulation studies[f]	X
Urinalysis[f]	X
Sweat chloride[g]	X
LCI (optional)[h]	X
Spirometry[i]	X
Medications review[j]	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)

BMI: body mass index; *CFTR*: *cystic fibrosis transmembrane conductance regulator* gene; ECG: electrocardiogram; ICF: informed consent form; LCI: lung clearance index

[a] If children 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. Refer to Section 11.4.3 for details.

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

[c] An ophthalmologic examination will be conducted by a licensed ophthalmologist. The examination does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the Screening Visit. Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination. Refer to Section 11.6.6 for details.

[d] 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. Refer to Section 11.6.5 for details.

[e] All subjects will be tested to assess *CFTR* genotype, regardless of availability of a previous *CFTR* genotype laboratory report. Refer to Section 11.6.2 for details. However, this assessment does not need to be repeated for confirmed subjects in Part A who may participate in Part B.

[f] Refer to Section 11.6.2 for details.

[g] If an eligible historical sweat chloride result is documented in the subject's medical record, that result alone (and not the Screening Visit result) may be used to determine eligibility. For subjects using an historical sweat chloride value documented in their medical record to determine eligibility, the sweat chloride test at the Screening Visit is still required. At screening, 2 samples may be collected, 1 sample from each arm (left and right).

[h] The LCI assessment (subjects ≥3 years of age at screening who consent/assent to the optional LCI Substudy) may be performed pre- or post-bronchodilator. The assessment will be performed in multiple replicates and before the spirometry assessment. Refer to Section 11.4.2 for details.

[i] Spirometry (subjects ≥3 years of age at screening only) may be performed pre- or post-bronchodilator. Refer to Section 11.6.7 for details.

[j] Refer to Section 9.4.2 for details.

Table 3-4 Study VX15-809-115: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period									Early Termination of Treatment (ETT) Visit[b]	Safety Follow-up Visit (Week 26 [2 weeks ± 4 days After Last Dose])[c,d]
	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)		
Clinic visit	X		X	X	X		X		X	X	X
Telephone contact[e]		X				X		X			
Stature and weight[f]	X		X	X	X		X		X	X	X
Vital signs[g]	X[h]		X	X	X		X		X	X	X
Pulse oximetry[g]	X		X	X	X		X		X	X	X
Ophthalmologic examination									X[i]	X[i]	X[i]

[a] All assessments will be performed before LUM/IVA dosing unless noted otherwise (Section 11.1). When repeats of an assessment are required postdose at a given visit, the assessment will be collected only once if LUM/IVA is not administered on the day of the visit (i.e., LUM/IVA interruption or permanent LUM/IVA discontinuation).

[b] Subjects who prematurely discontinue LUM/IVA treatment will be asked to complete the ETT Visit, to remain on study, and to complete the study assessments from the time of LUM/IVA treatment discontinuation through the Week 24 Visit and Safety Follow-up Visit, if applicable. The ETT Visit should be scheduled as soon as possible after the subject decides to terminate LUM/IVA treatment. 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. Subjects who become eligible to receive commercially-available LUM/IVA by prescription of a physician, and who choose to continue onto commercially-available LUM/IVA before completion of Part B, must remain on study-supplied LUM/IVA through the ETT Visit, and may only initiate treatment with commercially-available LUM/IVA after completion of this visit.

[c] The Safety Follow-up Visit is not required for subjects who permanently discontinue LUM/IVA treatment before or at the Week 16 Visit if they return for the Week 24 Visit. The Safety Follow-up Visit is not required for subjects who continue onto commercially-available LUM/IVA by prescription of a physician within 2 weeks (± 4 days) of completing LUM/IVA treatment at Week 24 or at the ETT Visit.

[d] The Safety Follow-up Visit, if applicable, is the last visit for Part B, and should also be the Day 1 Visit in the Extension Study (refer to Section 8.1.2 and the Extension Study for details).

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

[f] If children 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. Refer to Section 11.4.3 for details.

[g] The subject should rest for at least 5 minutes before having vital signs and pulse oximetry measured. Refer to 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 ophthalmologic examination will be conducted by a licensed ophthalmologist at the Week 24 Visit OR the Safety Follow-up Visit OR the ETT Visit, as applicable. Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination. Refer to Section 11.6.6 for details.

Table 3-4 Study VX15-809-115: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period									Early Termination of Treatment (ETT) Visit[b]	Safety Follow-up Visit (Week 26 [2 weeks ± 4 days After Last Dose])[c,d]
	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)		
Full physical examination[j]	X								X	X	X
Abbreviated physical examination	X[k]										
Standard 12-lead ECG[l]	X[m]		X	X	X		X		X	X	X
Serum chemistry[n]	X		X	X	X		X		X	X	X
Hematology[n]			X	X	X		X		X	X	
Coagulation studies[n]									X	X	
Urinalysis[n]	X								X	X	X
Qualitative microbiology cultures[o]	X								X		
PK sampling[p]			X	X					X		
Immunoreactive trypsinogen	X		X	X	X		X		X	X	X
Fecal elastase-1[q]	X		X	X	X		X		X	X	X
Sweat chloride[r]	X			X					X	X	X

j Symptom-directed physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator. Refer to Section 11.6.4 for details.

k An abbreviated physical examination will be performed 4 hours (± 30 minutes) postdose on Day 1. Refer to Section 11.6.4 for details.

l 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. Refer to Section 11.6.5 for details.

m Standard 12-lead ECGs will be performed predose and at 4 hours (± 15 minutes) postdose on Day 1. Predose ECGs on Day 1 will be performed in triplicate.

n Refer to Section 11.6.2 for details.

o Refer to Section 11.4.7 for details.

p At the Day 15 and Week 4 Visits, PK blood samples will be collected predose (within 60 minutes before dosing) and 2 to 6 hours after the morning dose. At the Week 24 Visit, PK blood samples will be collected at the same time as other blood collections. Refer to Section 11.3.1 for details.

q Samples 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 (Section 11.4.5). The sample may be collected pre- or postdose.

r The sweat chloride test must be conducted predose relative to the morning dose of LUM/IVA during the Treatment Period (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). Refer to Section 11.4.1 for details.

Table 3-4 Study VX15-809-115: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period									Early Termination of Treatment (ETT) Visit[b]	Safety Follow-up Visit (Week 26 [2 weeks ± 4 days After Last Dose])[c,d]
	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)		
LCI (optional)[s]	X			X					X	X	X
Spirometry[t]	X[u]		X	X	X		X		X	X	X
Other events related to outcome[v]	X		X	X	X	X	X	X	X	X	
LUM/IVA dosing[w]	LUM/IVA q12h										
Observation 4 hours after the first dose	X										
Acceptability/palatability assessment[x]	X										
Study drug count			X	X	X		X		X	X	
Medications, treatments, and procedures review[y]	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; CF: cystic fibrosis; ECG: electrocardiogram; ETT: Early Termination of Treatment; ICF: informed consent form; IVA: ivacaftor; LCI: lung clearance index; LUM: lumacaftor; PK: pharmacokinetic; q12h: every 12 hours

[s] The LCI assessment (subjects ≥3 years of age at screening who consent/assent to the optional LCI Substudy) should be performed pre-bronchodilator and before LUM/IVA dosing (Section 11.4.2). The assessment will be performed in multiple replicates and before the spirometry assessment.

[t] Spirometry (subjects ≥3 years of age at screening only) should be performed pre-bronchodilator. Refer to Section 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 such as a standard CF high-fat, high-calorie meal or snack (Section 10.2). On days of scheduled visits, the morning dose of LUM/IVA will be administered at the site after predose assessments have been completed. At the Week 24 Visit, the morning dose of LUM/IVA will NOT be administered. The last dose of LUM/IVA in Part B will be the evening dose administered the day before the Week 24 Visit.

[x] Refer to Section 11.4.9 for details.

[y] Refer to Section 9.4.2 for details.

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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 United States (US),[1,2] 32,000 individuals in the European Union (EU),[3] 4,100 individuals in Canada,[4] and 3,200 individuals in Australia.[5] The incidence and prevalence of CF varies between racial groups. For example, CF is considerably more common in the Caucasian populations of North America and Europe than in Asian and African populations.[2,3] Based on the size of the population, CF qualifies as an orphan disease.[6,7] 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.[2,8,9] Although the disease affects multiple organs, progressive loss of lung function is the leading cause of mortality.[10]

Cystic fibrosis is caused by a defect in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), an epithelial chloride (Cl^-) ion channel activated by cyclic AMP-dependent protein kinase A that is responsible for aiding in the regulation of salt and water absorption and secretion in various tissues.[11] This function is defective in patients with CF due to a loss of either cell surface expression and/or function of CFTR.

More than 2000 mutations in the *CFTR* gene have been identified.[12] The most prevalent mutation is an in-frame deletion in the *CFTR* gene resulting in a loss of phenylalanine at position 508 in the wild-type CFTR protein (F508del-CFTR).[13] The proportion of patients with CF who are homozygous for the *F508del-CFTR* mutation is similar across geographic regions: approximately 47% in the US[2], 44% in the EU[3], 50% in Canada[4], and 51% in Australia.[5] The *F508del-CFTR* mutation interferes with the ability of the CFTR protein to reach and remain at the cell surface, as well as to open and close, resulting in decreased Cl^- transport.[14,15] Because of the near-complete loss of CFTR chloride transport, the *F508del/F508del* mutation is typically associated with a severe form of CF, characterized by a rapid rate of lung function decline, colonization with *Pseudomonas aeruginosa*, a high incidence of pancreatic insufficiency, and reduced life expectancy.[16,17,18,19]

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

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

LUM and IVA in combination is the first medicine designed to treat the underlying molecular defect and enhance the function of CFTR in patients homozygous for *F508del*. The LUM/IVA development program targets patients with CF who have the *F508del* mutation, the most common mutation in the *CFTR* gene.

Details about the LUM/IVA development program can be found in the Investigator's Brochure.[20]

5.2 Study Rationale

CF greatly affects the pediatric population, as approximately half of the total CF population is less than 18 years of age.[21] 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 present study is designed to obtain pharmacokinetic (PK) and safety information to support a proposed indication expansion of LUM/IVA in subjects 2 through 5 years of age, homozygous for *F508del*.

6 STUDY OBJECTIVES

6.1 Primary Objectives

Part A

To evaluate the PK of LUM and IVA and their respective metabolites in subjects aged 2 through 5 years with CF, homozygous for *F508del*

Part B

To evaluate the safety of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for *F508del*

6.2 Secondary Objectives

Part A

To evaluate the safety of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for *F508del*

Part B

- To evaluate the pharmacodynamics (PD) of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for *F508del*

- To evaluate the off-drug PD response after the Washout Period
- To evaluate the PK of LUM and IVA and their respective metabolites in subjects aged 2 through 5 years with CF, homozygous for *F508del*

7 STUDY ENDPOINTS

7.1 Primary Endpoints

Part A

PK parameters of LUM and IVA

Part B

Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis), standard 12-lead electrocardiograms (ECGs), vital signs, pulse oximetry, ophthalmological examinations, and spirometry

7.2 Secondary Endpoints

Part A

- PK parameters of the metabolites of LUM and IVA
- Safety and tolerability assessments based on AEs, clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis), standard 12-lead electrocardiograms (ECGs), vital signs, pulse oximetry, and spirometry

Part B

- Absolute change from baseline in sweat chloride at Week 24
- Absolute change from baseline in body mass index (BMI) and BMI-for-age z-score at Week 24
- Absolute change from baseline in weight and weight-for-age z-score at Week 24
- Absolute change from baseline in stature and stature-for-age z-score at Week 24
- Time-to-first pulmonary exacerbation through Week 24
- Number of pulmonary exacerbations through Week 24
- Number of CF-related hospitalizations through Week 24
- Absolute change in fecal elastase-1 (FE-1) levels from baseline at Week 24
- Absolute change in serum levels of immunoreactive trypsinogen (IRT) from baseline through Week 24
- Change in microbiology cultures from baseline at Week 24
- Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at Week 24

- Absolute change in sweat chloride from Week 24 at Week 26
- Acceptability/palatability of LUM/IVA granules at Day 1
- Absolute change from baseline in lung clearance index $(LCI)_{2.5}$ at Week 24
- Absolute change from baseline in $LCI_{5.0}$ at Week 24
- PK parameters of LUM, IVA, and their respective metabolites

8 STUDY DESIGN

8.1 Overview of Study Design

This is a Phase 3, 2-part, open-label, multicenter study evaluating the PK, safety, tolerability, and PD of multiple doses of LUM/IVA in subjects 2 through 5 years of age (inclusive) with CF, homozygous for *F508del*. Subjects who participate in Part A may participate in Part B, if they meet the eligibility criteria.

8.1.1 Part A

Approximately 12 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 10 subjects should complete Part A. Approximately half of the subjects should complete the study in each of the following weight groups: <14 kg and ≥14 kg at screening.

Part A includes the following:

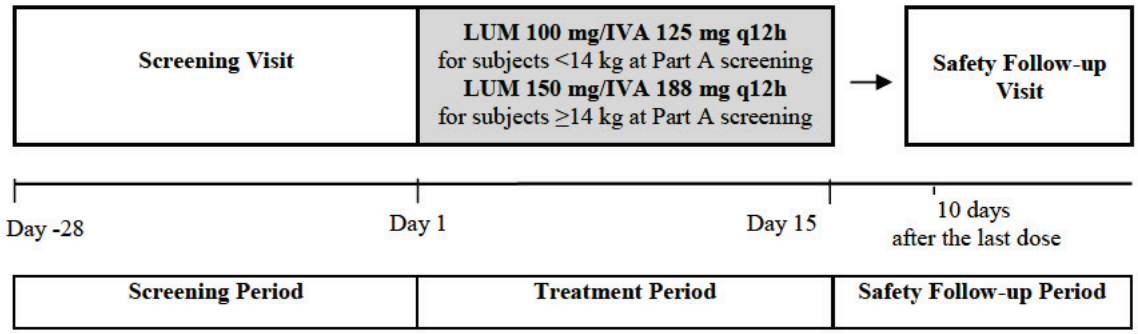
- Screening Period (Day -28 through Day -1)
- Treatment Period (Day 1 through Day 15 ± 2 days)
- Safety Follow-up Visit (10 ± 3 days after the last dose of LUM/IVA)

Figure 8-1 depicts the schematic for the Part A study design. Procedural details are described in the following sections:

- Section 10.2.1 for dose administration;
- Section 8.1.3 for the Screening Period;
- Section 8.1.7.1 for the Treatment Period;
- Section 8.1.9.1 for the Safety Follow-up; and
- Section 8.1.10.1 for early discontinuation.

A review of safety, tolerability, and available PK data will be completed by an internal Vertex Pharmaceuticals Incorporated (Vertex) team after Part A to determine the dose(s) to be evaluated in Part B. Additional subjects or treatment cohorts may be enrolled, if data from the initial, planned, 12 subjects are inadequate to make a determination of the dose(s) to be evaluated in Part B.

Figure 8-1 Schematic of Study Design for Part A



IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours
Notes: Approximately half of the subjects should complete the study in each of the following weight groups: <14 kg and ≥14 kg at screening. No dose adjustments will be made across the duration of study treatment. On Day 15, only the morning dose of LUM/IVA will be administered.

8.1.2 Part B

Approximately 56 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 50 subjects should complete Part B; at least 10 subjects must be <3 years of age at screening. Subjects should be ≥3 years of age at screening for enrollment in the optional LCI Substudy at a subset of sites. Additional subjects may be enrolled at the sponsor's discretion to achieve up to 30 subjects in the LCI Substudy.

Part B includes the following:

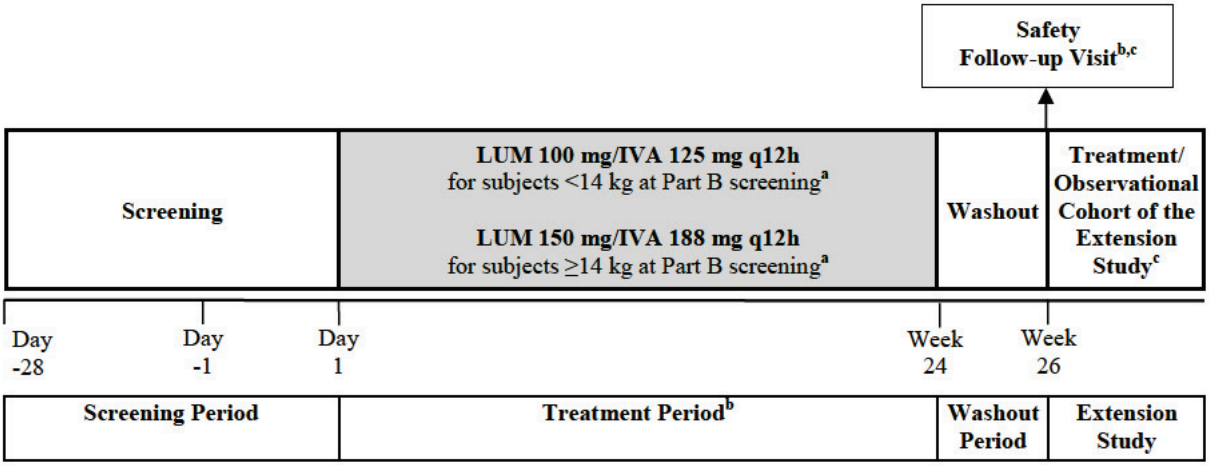
- Screening Period (Day -28 through Day -1)
- Treatment Period (Day 1 through Week 24 ± 5 days)
- Washout Period (Week 24 to Week 26 ± 4 days)
- Safety Follow-up Visit (Week 26 [2 weeks ± 4 days after the last study dose of LUM/IVA])

Figure 8-2 depicts the schematic for the Part B study design. Procedural details are described in the following sections:

- Section 10.2.2 for dose administration;
- Section 8.1.3 for the Screening Period;
- Section 8.1.7.2 for the Treatment Period;
- Section 8.1.8.2 for the Washout Period;
- Section 8.1.9.2 for the Safety Follow-up; and
- Section 8.1.10.2 for Early Termination of Treatment (ETT).

Subjects who have completed the required visits in Part B may be eligible to enroll in the Treatment Cohort or Observational Cohort of an Extension Study to evaluate long-term treatment with LUM/IVA; enrollment will be based on the eligibility criteria. The Treatment Cohort will enroll subjects who completed LUM/IVA treatment and the Safety Follow-up Visit in Part B. The Observational Cohort will enroll subjects who received at least 4 weeks of LUM/IVA treatment in Part B and completed visits up to the Safety Follow-up Visit, if applicable, in Part B, but do not meet eligibility criteria for enrollment into the Treatment Cohort. The Safety Follow-up Visit, if applicable, is the last visit for Part B, and should also be the Day 1 Visit in the Extension Study.

Figure 8-2 Schematic of Study Design for Part B



ETT: Early Termination of Treatment; IVA: ivacaftor; LCI: lung clearance index; LUM: lumacaftor; q12h: every 12 hours
Notes: Approximately 56 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 50 subjects should complete Part B; at least 10 subjects must be <3 years of age. Subjects should be ≥3 years of age for enrollment in the optional LCI Substudy at a subset of sites. Additional subjects may be enrolled at the sponsor's discretion to achieve up to 30 subjects in the LCI Substudy.

[a] The doses listed above are the planned doses for Part B. Depending on the results from Part A, a single dose from Part A may be selected for all subjects in Part B or a previously unspecified dose or doses may be selected for Part B. No dose adjustments across the duration of treatment will be made. The last dose of LUM/IVA in Part B will be the evening dose before the Week 24 Visit.

[b] Subjects who prematurely discontinue LUM/IVA treatment will be asked to complete the ETT Visit, to remain on study, and to complete the study assessments from the time of LUM/IVA discontinuation through the Week 24 Visit and the Safety Follow-up Visit, if applicable. The Safety Follow-up Visit is not required for subjects who permanently discontinue LUM/IVA treatment before or at the Week 16 Visit if they return for the Week 24 Visit or for subjects who continue onto commercially-available LUM/IVA by prescription of a physician within 2 weeks (± 4 days) of completing LUM/IVA treatment at Week 24 or at the ETT Visit.

[c] Subjects who have completed the required visits in Part B may be eligible to enroll in the Treatment Cohort or Observational Cohort of an Extension Study to evaluate long-term treatment with LUM/IVA; enrollment will be based on the eligibility criteria.

8.1.3 Screening

Part A and Part B

Screening Visit assessments are listed in Table 3-1 for Part A and Table 3-3 for Part B.

For Parts A and B, the Screening Period will occur within 28 days before the first dose of LUM/IVA to confirm that subjects meet the selection criteria for the corresponding part in the study. To participate in either part of the study, the subject's parent or legal guardian must sign and date a study-specific informed consent form (ICF) and the subject must sign an assent form (if applicable) before any study-specific procedures can be performed. The ICF (and assent form, if applicable) will comply with all applicable regulations governing the protection of human subjects and will be approved by Vertex and the site's institutional review board (IRB).

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

8.1.4 Repetition of Screening Assessments

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

- If there is clear evidence of a laboratory error (e.g., hemolyzed sample), equipment malfunction, or technician error, collection of a repeat sample for the appropriate laboratory test may be permitted after discussion with the Vertex medical monitor or authorized designee.
- Exclusionary liver function test (LFT) levels, which may be retested within 14 days of the original Screening Visit date.

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

8.1.5 Rescreening

Subjects may be rescreened after discussion with the Vertex medical monitor or authorized designee; all rescreening requires Vertex approval. If a subject is rescreened, all Screening Visit assessments will be repeated except for CF genotyping and the ophthalmologic examination (if performed within the last 3 months before the Screening Visit). Subjects may only be rescreened once per study part. If a subject is rescreened, the new screening window date will begin once the first rescreening assessment has been initiated.

8.1.6 Extension of Screening Period Window

A subject may have the Screening Period window extended by 1 week after approval by the medical monitor or authorized designee for the following reasons:

- Repetition of the Screening Period assessments (Section 8.1.4)
- Scheduling of the ophthalmologic examination (Section 11.6.6)
- Availability or malfunction of required equipment or technician error.

8.1.7 Treatment Period

Treatment Period assessments are listed in Table 3-2 for Part A and Table 3-4 for Part B.

8.1.7.1 Part A

The Part A Treatment Period is 15 days; LUM/IVA will be administered every 12 hours (q12h) from Day 1 through Day 15. The morning LUM/IVA dose on Day 15 will be the last dose in Part A. LUM/IVA administration and management details are provided in Section 10.

Study visits during the Treatment Period will occur as shown in Table 3-2. Subjects will be outpatients during the Treatment Period. All visits should occur within the windows specified.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled visit, the Vertex medical monitor or authorized designee will be notified, and the investigator will make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

Procedures for subjects who prematurely discontinue LUM/IVA treatment are described in Section 8.1.10.1.

8.1.7.2 Part B

The Part B Treatment Period is 24 weeks; LUM/IVA will be administered q12h from Day 1 through Week 24. The evening LUM/IVA dose before the Week 24 Visit will be the last dose in Part B. LUM/IVA administration and management details are provided in Section 10.

Study visits during the Treatment Period will occur as shown in Table 3-4. Subjects will be outpatients during the Treatment Period. All visits should occur within the windows specified.

Procedures for subjects who prematurely discontinue LUM/IVA treatment are described in Section 8.1.10.2.

8.1.8 Washout Period

8.1.8.1 Part A

Not applicable

8.1.8.2 Part B

A 2-week Washout Period (Week 24 to Week 26 ± 4 days) will be included in order to evaluate the off-drug PD response.

8.1.9 Follow-up

8.1.9.1 Part A

Table 3-2 lists the Safety Follow-up Visit assessments for Part A. Subjects will have a Safety Follow-up Visit 10 (± 3) days after the last dose of LUM/IVA.

8.1.9.2 Part B

Table 3-4 lists the Safety Follow-up Visit assessments for Part B. The Safety Follow-up Visit is scheduled to occur 2 weeks (± 4 days) after the last dose of LUM/IVA.

The Safety Follow-up Visit, if applicable is the last visit for Part B, and should also be the Day 1 Visit in the Extension Study.

The Safety Follow-up Visit is not required for subjects who continue onto commercially-available LUM/IVA by prescription of a physician within 2 weeks (± 4 days) of completing LUM/IVA treatment at Week 24 or at the ETT Visit.

The Safety Follow-up Visit is not required for subjects who permanently discontinue LUM/IVA treatment before or at the Week 16 Visit if they return for the Week 24 Visit.

8.1.10 Early Discontinuation/Early Termination of Treatment

8.1.10.1 Part A

Subjects who permanently discontinue LUM/IVA treatment for any reason (except withdrawal of consent) will be asked to return to the clinical site 10 (± 3) days after their last dose of LUM/IVA. The assessments to be performed at this visit will be the same as those for the Safety Follow-up Visit (Table 3-2).

8.1.10.2 Part B

Subjects who prematurely discontinue LUM/IVA treatment will be asked to complete the ETT Visit as soon as possible after their last dose, to remain on study, and to complete the study assessments from the time of LUM/IVA treatment discontinuation through the Week 24 Visit and the Safety Follow-up Visit, if applicable. The assessments to be completed are shown in Table 3-4. 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, if applicable (i.e., the assessments performed will be those specified for the ETT Visit), and a Safety Follow-up Visit will not be required.

Subjects who become eligible to receive commercially-available LUM/IVA by prescription of a physician, and who choose to continue onto commercially-available LUM/IVA before completion of Part B, must remain on study-supplied LUM/IVA through the ETT Visit, and may only initiate treatment with commercially-available LUM/IVA after completion of this visit.

8.2 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) is planned for Part B only. Before the start of Part B, the IDMC may be consulted at the discretion of the sponsor. The IDMC objectives and operational details will be defined in a separate document (the IDMC Charter), which will be finalized before the first subject is enrolled in Part B. The IDMC will conduct regular planned reviews of study data for the purpose of safety monitoring as outlined in the IDMC Charter.

8.3 Rationale for Study Design and Study Drug Regimens

8.3.1 Study Design

This is a Phase 3, 2-part, open-label, multicenter study in subjects 2 through 5 years of age (inclusive) with CF who are homozygous for *F508del.*

Part A will evaluate the PK and safety of LUM/IVA over 15 days of dosing. The evaluation of LUM/IVA as multiple doses allows for the assessment of the time-dependent induction effect of LUM on IVA. The duration of dosing in Part A was selected to evaluate the PK and safety endpoints when the induction effect of LUM on the metabolism of IVA was

anticipated to have reached steady-state. Part B is designed to evaluate the safety of LUM/IVA dosing over 24 weeks in this pediatric CF population. In addition, the PD effects and PK of multiple doses of LUM/IVA over 24 weeks of dosing will be evaluated.

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.[22] 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]). The present study is designed to obtain PK and safety information to support a proposed indication expansion of LUM/IVA in subjects 2 through 5 years of age, homozygous for *F508del*. The open-label design is considered adequate to evaluate the PK and safety of LUM/IVA in this pediatric population.

This design is consistent with ICH guidelines for the study of human subjects, especially children, and balances safety concerns with potential benefits for the individual.

8.3.2 Study Drug Dose and Duration

Rationale for Dose

Part A of this study 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 Part A is intended to inform the appropriateness or necessary adjustment of planned doses for Part B. 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 the study population. The IVA model was coupled to the LUM model to account for the induction of cytochrome P450 (CYP)3A by LUM, which increases the metabolism of IVA. Thus, the IVA clearance is impacted by the weight dependence for the clearance of IVA alone and LUM exposure dependence induction effect. The population PK model is based on data obtained from subjects 6 years of age and older across the LUM and IVA combination development program.

In the combination program, the dose regimen of LUM 400 mg/IVA 250 mg q12h was used in the Phase 3 studies (Studies 103 and 104) for subjects 12 years of age and older. In the Phase 3 Study 011, the dose regimen of LUM 200 mg/IVA 250 mg q12h was used for subjects 6 through 11 years of age. The LUM and IVA exposures from these studies are summarized in Table 8-1. For subjects 2 through 5 years of age who weigh less than 14 kg, oral administration of 100 mg LUM is projected to yield a mean area under the concentration-time curve as steady state (AUC_{ss}) of 201 µg/mL*h. For subjects 2 through 5 years of age who weigh 14 kg or greater, oral administration of 150 mg LUM is projected to yield a mean AUC_{ss} of 238 µg/mL*h. Based on simulations for subjects 2 through 5 years of age, the LUM doses selected for Part A are expected to yield exposures that are comparable to those of subjects 6 years of age and older, which has been shown to be safe and well-tolerated in combination with IVA.

IVA as a single agent was previously investigated and approved for use in pediatric patients with CF 2 to less than 6 years of age with select mutations. In the Phase 3 study for this population, pediatric subjects who weighed less than 14 kg received oral administration of IVA granules, 50 mg q12h, and had a mean AUC_{ss} of 10.5 µg/mL*h; pediatric subjects 2 to less than 6 years of age who weighed 14 kg or greater received IVA granules, 75 mg q12h, and had a mean AUC_{ss} of 11.3 µg/mL*h. In the combination program, due to the induction effect of LUM on the metabolism of IVA, the IVA exposures are lower than that of the IVA monotherapy. The IVA AUC_{ss} for subjects 6 years of age and older in the combination program are summarized in Table 8-1. For subjects 2 through 5 years of age who weigh less than 14 kg, oral administration of 125 mg IVA in combination with LUM is projected to yield a mean AUC_{ss} of 5.49 µg/mL*h. For subjects 2 through 5 years of age who weigh 14 kg or greater, oral administration of 188 mg IVA in combination with LUM is projected to yield a mean AUC_{ss} of 5.71 µg/mL*h. Based on simulations for subjects 2 through 5 years of age, the IVA doses selected for Part A are expected to yield IVA exposures that are comparable to subjects 6 years of age and older and within prior clinical experience with IVA alone and IVA given in combination with LUM.

Table 8-1 Summary of LUM and IVA Exposures in Subjects With CF Who Are 6 Years of Age and Older

		LUM $AUC_{0\text{-}12h}$ (hr·µg/mL)	IVA $AUC_{0\text{-}12h}$ (hr·µg/mL)
Age Group	**N**	**Mean (SD)**	**Mean (SD)**
6 through 11 years (pediatrics)	62	203 (57.4)	5.26 (3.08)
12 through 17 years (adolescents)	98	241 (61.4)	3.90 (1.56)
18 years and older (adults)	265	216 (47.9)	3.80 (1.94)

$AUC_{0\text{-}12h}$: area under the concentration-time curve from 0 to12 hours; IVA: ivacaftor; LUM: lumacaftor; PK: pharmacokinetic; q12h: every 12 hours; SD: standard deviation
Note: PK data are from Study 011 Part B (6 through 11 years of age) and Studies 103 and 104 (12 through 17 years of age; 18 years of age and older). Subjects in Study 011 received LUM 200 mg/IVA 250 mg q12h for 24 weeks and subjects in Studies 103 and 104 received LUM 400 mg/IVA 250 mg q12h for 24 weeks.

No safety issues were identified in prior clinical or nonclinical studies that would preclude the dosing regimen proposed for the current protocol.

Rationale for the Duration of Dosing

The concentration-time course of LUM in combination with IVA was studied in prior drug-drug interaction studies (Studies VX08-809-005 and VX10-809-006). When given in combination, LUM is expected to cause time-dependent induction of IVA metabolism. The duration of 15 days was selected for Part A to evaluate PK, safety, and tolerability when the induction effect of LUM on the metabolism of IVA is anticipated to have reached steady-state.

The duration of 24 weeks for Part B will provide an adequate assessment of safety in this population.

8.3.3 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. Ophthalmologic examinations and spirometry assessments were added to the standard safety assessments. In addition, assessments were added to evaluate the PD effects of LUM/IVA and the acceptability/palatability of LUM/IVA granules.

Ophthalmologic Examinations: A juvenile rat toxicity study performed to support dosing of IVA in subjects <2 years of age demonstrated lens opacities in some animals.[20] 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 ophthalmologic examinations 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, the spirometry testing will only be performed on subjects who are ≥3 years of age at screening. 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.[23,24] Studies have shown that 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.[25,26] Furthermore, 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.[27] Therefore, only subjects who are ≥3 years of age at screening and who consent/assent to the optional LCI Substudy will undergo the LCI assessments, and LCI will only be done at selected sites that have the capability to perform these assessments.

Weight, Stature, and BMI: Malnutrition is common in patients with CF because of increased energy expenditures due to lung disease and fat malabsorption. Given that LUM/IVA is a systemic therapy, it has the potential to improve extrapulmonary manifestations of CF, including those in the gastrointestinal system. Improved nutritional status, defined as an increase in weight and/or BMI, is considered an appropriate endpoint for therapies targeting exocrine pancreatic manifestation of CF and was explored in previous clinical studies of CFTR-targeted therapies (Studies 103 and 104).

As children gain weight and stature as part of normal growth, adjustment for age and sex is necessary to assess changes in nutritional status in a population of boys and girls in varying

stages of growth. To evaluate the effect of LUM/IVA on growth and nutrition adjusted for age and sex, respective weight, stature, and BMI z-scores will be determined. Stature and weight will be collected at the study visits indicated in the Schedule of Assessments.

Sweat Chloride: In patients with CF, the underlying CFTR ion transport defect results in elevated sweat electrolyte levels.[28,29] The sweat chloride test (quantitative pilocarpine iontophoresis) is the most common diagnostic tool for CF. A sweat chloride concentration of ≥60 mmol/L is considered to be diagnostic of CF, whereas <40 mmol/L is considered normal. Based on the mechanism of action of LUM and IVA, the sweat chloride test was included in this study as a measure of the PD effect of LUM/IVA on CFTR activity.

Other Events Related to Outcome: These assessments (pulmonary exacerbations, administration of antibiotic therapy for sinopulmonary signs and symptoms, and hospitalizations) are other outcomes used to assess efficacy in therapies targeting improvement in CF disease. CF pulmonary exacerbations are a compilation of patient signs and symptoms that often result in the need for aggressive treatment, including the use of intravenous (IV) antibiotics that may require hospitalization. To date, there is no generally accepted objective definition of a pulmonary exacerbation,[30] and large multicenter CF clinical studies have used many variations of physician-derived definitions.[31,32,33,34] Despite the lack of a standard definition, reduction in pulmonary exacerbation rate has served as a key clinical efficacy measure in definitive CF clinical studies, supporting the registration of 2 chronic CF pulmonary therapies (inhaled recombinant human DNase and inhaled tobramycin).[30] To evaluate the potential effect of LUM/IVA on pulmonary exacerbations, count, duration, and time-to-first event of hospitalizations and count and time-to-first event of IV courses of antibiotics for pulmonary exacerbations will be derived. For data consistency, this protocol specifies 1 definition of pulmonary exacerbation, which is based on the definition used for the other studies including the IVA monotherapy initial registration studies (Section 11.4.4.1). Because signs and symptoms in the definition may occur without meeting the overall definition of a pulmonary exacerbation, the number and timing of outpatient sick visits to the clinic or hospital for CF that are unrelated to the study protocol will also be collected.

Exocrine Pancreatic Function: The pancreas is 1 of the earliest and most seriously affected organs in patients with CF who have 2 copies of the *F508del* mutation, a high fraction of which develop pancreatic insufficiency (PI).

- 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.[35] 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 during the study for evaluations of 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 2 through 5 years of age do not expectorate spontaneously, oropharyngeal swabs will be used to obtain airway cultures in this study.

Acceptability/palatability measures: All subjects in Part B will have their acceptance of the dose administered recorded. The reaction of the subject will be assessed by the investigator or authorized designee as described in Section 11.4.9.

9 STUDY POPULATION

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

9.1 Inclusion Criteria

Part A and Part B

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

1. Subject's legally appointed and authorized representative (e.g., parent or legal guardian) will sign and date an ICF and the subject will sign and date an assent form (if applicable).
2. Subject's legally appointed and authorized representative (e.g., parent or legal guardian) is willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, and other study procedures.
3. Subjects (males and females) will be between 2 and 5 years of age, inclusive, on the date of informed consent (and assent, if applicable) for the relevant study part.
4. Subjects who weigh ≥8 kg without shoes and wearing light clothing at the Screening Visit.
5. Subjects with confirmed diagnosis of CF[36] at the Screening Visit. CF is defined as:
   - 2 CF-causing mutations (all as documented in the subject's medical record) AND
   - chronic sinopulmonary disease OR gastrointestinal/nutritional abnormalities; OR
   - **Part B only**: a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis as documented in the subject's medical record OR from the sweat chloride test result obtained at the Screening Visit. If an eligible historical sweat chloride result is documented in the subject's medical record, that result alone [and not the Screening Visit result] may be used to determine eligibility.

6. Subjects who are homozygous for *F508del* (genotype to be confirmed at the Screening Visit). If the *CFTR* screening genotype result is not received before Day -1, a previous *CFTR* genotype laboratory report may be used to establish eligibility. Note:
   - Subjects who have been enrolled and whose screening genotype does not confirm study eligibility must be discontinued from the study, as described in Section 9.5.
   - This assessment does not need to be repeated for confirmed subjects in Part A who may participate in Part B.
7. Subjects with stable CF disease as deemed by the investigator at the Screening Visit.
8. Subjects who are willing to remain on a stable CF medication regimen through Day 15 (**Part A**) or through the Safety Follow-up Visit (**Part B**), if applicable.

9.2 Exclusion Criteria

Part A and Part B

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

1. History of any comorbidity reviewed at the Screening Visit that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering LUM/IVA to the subject. For example, a history of cirrhosis with portal hypertension.
2. Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject (as deemed by the investigator).
3. Any of the following abnormal laboratory values at the Screening Visit:
   - Hemoglobin <10 g/dL
   - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin >2 × upper limit of normal (ULN)
   - Abnormal renal function defined as glomerular filtration rate ≤45 mL/min/1.73 m^2 (calculated by the Bedside Schwartz equation)[37]
4. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of LUM/IVA).
5. A standard 12-lead ECG demonstrating QTc >450 msec at the Screening Visit. If QTc exceeds 450 msec at the Screening Visit, the ECG should be repeated 2 more times during the Screening Period, and the average of the 3 QTc values should be used to determine the subject's eligibility.
6. History of solid organ or hematological transplantation.

7. Ongoing or prior participation in an investigational drug study (including studies investigating LUM and/or IVA) within 30 days of the Screening Visit.
   - A washout period of 5 terminal half-lives of the previous investigational study drug, or 30 days, whichever is longer, must elapse before the Screening Visit.
   - The duration of the elapsed time may be longer if required by local regulations.

   Note: Ongoing participation in a noninterventional study (including observational studies) is permitted.
8. Use of restricted medication or food within specified duration before the first dose of LUM/IVA as defined in Section 9.3.
9. History of cataract/lens opacity or evidence of cataract/lens opacity determined to be clinically significant by a licensed ophthalmologist during the ophthalmologic examination at the Screening Visit. The Screening Visit ophthalmologic examination does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the Screening Visit (Section 11.6.6). Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination and this criterion does not apply.
10. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study.

9.3 Study Restrictions

Part A

Prohibited medications and certain foods are not allowed during the time periods summarized in Table 9-1.

A nonexhaustive list of study prohibitions and cautions for food and medication will be provided in the study reference manual.

Table 9-1 Study Restrictions – Part A

	Study Period	
Restricted Medication/Food[a]	**Screening Period**	**Treatment Period**
Moderate and strong CYP3A inhibitors and inducers	None allowed within 14 days before the first dose of LUM/IVA	None allowed until after the Safety Follow-up Visit
Grapefruit/grapefruit juice, pomelos, star fruit, Seville oranges	None allowed within 14 days before the first dose of LUM/IVA	None allowed until last PK sample is taken

CYP: cytochrome P450; IVA: ivacaftor; LUM: lumacaftor; PK: pharmacokinetics
Note: The use of restricted medication in subjects with a medical need will be addressed on a case-by-case basis with the medical monitor or authorized designee.
[a] See Section 9.4 for guidance for concomitant medications.

Part B

Prohibited medications and certain foods are not allowed (Screening Period through Week 24 of Part B) as summarized in Table 9-2.

A nonexhaustive list of study prohibitions and cautions for food and medication will be provided in the study reference manual.

Table 9-2 Study Restrictions – Part B

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

CYP: cytochrome P450; IVA: ivacaftor; LUM: lumacaftor
Note: The use of restricted medication in subjects with a medical need will be addressed on a case-by-case basis with the medical monitor or authorized designee.
[a] See Section 9.4 for guidance for concomitant medications.

9.4 Prior and Concomitant Medications

9.4.1 Prohibited Medications

Part A and Part B

The prohibited medications that are described for Part A and Part B in Section 9.3 are not allowed in this study while subjects are receiving LUM/IVA.

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

The use of CYP2C and 2B6 substrates are not prohibited in this study, 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 such drugs with LUM and IVA during this study and discuss the use of these substrates during this study with the medical monitor or authorized designee.

A nonexhaustive list of study prohibitions and cautions for food and medications will be provided in the study reference manual.

9.4.2 Prior and Concomitant Medications

Part A and Part B

Information regarding all prior and concomitant medications, including the subject's CF medications, other medications, and herbal and naturopathic remedies administered from 28 days before the first dose through the Safety Follow-up Visit will be recorded in each subject's source documents. In addition, concomitant medication dose(s) may be collected.

- It is recommended that subjects remain on a stable medication regimen for their CF from 28 days before Day 1 through Day 15 (**Part A**), through the Safety Follow-up Visit (**Part B**), if applicable. 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.
- While the etiology of respiratory events associated with LUM/IVA is not yet known, data from healthy subjects in Study VX12-809-009 Cohort 4 suggest that treatment with short-acting bronchodilators may reverse the initial transient decline in $ppFEV_1$ when dosed with LUM/IVA. Subjects in **Part B** will be prescribed a short-acting bronchodilator (if not already prescribed) to ensure constant availability during the study.
- Information about bronchodilator use during the study will be collected and documented in the subject's source documents. Subjects who are using a bronchodilator should have their spirometry assessments performed according to the guidelines provided in Section 11.6.7.

9.5 Removal of Subjects

Part A and Part B

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 LUM/IVA 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 LUM/IVA treatment in Part B, the subject will continue to be followed and should continue to return for study assessments as noted in Section 8.1.10, 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 or Safety Follow-up Visit, as applicable (see Sections 8.1.8 and 8.1.10), and follow up with the subject regarding any unresolved AEs.

If a subject/caregiver withdraws consent, 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.

Part A and Part B: Removal of subjects due to *CFTR* genotype

Subjects who are enrolled on the basis of a historical genotype result (see Section 9.1, Inclusion Criterion # 6), and whose screening genotype does not confirm study eligibility,

will be discontinued from LUM/IVA treatment, undergo the ETT and/or Safety Follow-up Visits, as per Sections 8.1.8 and 8.1.10, and will then be discontinued from the study. After LUM/IVA treatment discontinuation, these subjects will not undergo any further assessments other than those performed at the ETT and/or Safety Follow-up Visit(s).

9.6 Replacement of Subjects

Part A

Subjects who withdraw or are withdrawn for non-safety reasons during the Treatment Period may be replaced in order to have an adequate number of subjects complete the study.

Part B

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

10 STUDY DRUG ADMINISTRATION AND MANAGEMENT

10.1 Preparation and Dispensing

Part A and Part B

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) for administration to the study subject.

10.2 Administration

10.2.1 Part A

On Day 1 through the morning dose on Day 15 (last dose of LUM/IVA), LUM/IVA granules will be orally administered with the approved foods and liquids listed in the study manual (e.g., apple sauce), as shown in Table 10-1.

Table 10-1 Study Drug Administration – Part A

Dose	Time	LUM/IVA (Number of capsules)
Subject screening weight <14 kg[a] LUM 100 mg/IVA 125 mg q12h	AM	1 capsule
	PM	1 capsule
Subject screening weight ≥14 kg[a] LUM 150 mg/IVA 188 mg q12h	AM	2 capsules
	PM	2 capsules

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

[a] Doses are based on the subject's weight at screening; no dose adjustments will be made across the duration of study treatment.

LUM/IVA will be administered approximately 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. The morning LUM/IVA dose will be administered at the clinical site on Days 1, 8, and 15.
2. In the event that a subject's scheduled visit occurs in the afternoon, all assessments will be collected relative to the evening dose.
3. LUM/IVA will be administered after all predose safety and PK assessments have been performed.
4. All LUM/IVA doses (morning and evening, as applicable) should be administered at approximately every 12 hours (± 1 hour) on each dosing occasion (e.g., if the morning dose is administered at 08:00 on Day 1, all subsequent morning doses should be administered between 07:00 and 09:00).
5. The granule formulation will be dispensed by opening the capsules containing the granules and mixing the granules with the approved foods and liquids listed in the study manual (e.g., apple sauce). Each dose (LUM 100 mg/IVA 125 mg or LUM 150 mg/IVA 188 mg) will be comprised of the approved food or liquids into which the granules from the capsules are mixed. Details on preparing LUM/IVA will be provided in the pharmacy manual.
6. At the Day 1 Visit, all subjects will be observed for 4 hours after the morning LUM/IVA dose.
7. The morning dose on Day 15 will be the last LUM/IVA dose.

10.2.2 Part B

A review of safety, tolerability, and available PK data will be completed by an internal Vertex team after Part A to determine the dose(s) chosen for evaluation in Part B (Section 8.3.2). The planned doses are listed in Table 10-2. However, depending on the results from Part A, a single dose from Part A may be selected for all Part B subjects or a previously unspecified dose or doses may be selected for Part B.

On Day 1 through the evening dose before the Week 24 Visit (last dose of LUM/IVA), LUM/IVA granules will be orally administered with the approved foods and liquids listed in the study manual (e.g., apple sauce), as shown in Table 10-2.

Table 10-2 Study Drug Administration – Planned Doses for Part B

Proposed Doses[a]	Time	LUM/IVA (Number of stick packs)
Subject screening weight <14 kg[b] LUM 100 mg/IVA 125 mg q12h	AM	1 stick pack
	PM	1 stick pack
Subject screening weight ≥14 kg[b] LUM 150 mg/IVA 188 mg q12h	AM	1 stick pack
	PM	1 stick pack

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

[a] The doses listed above are the planned doses for Part B. Depending on the results from Part A, a single dose from Part A may be selected for all Part B subjects or a previously unspecified dose or doses may be selected for Part B.

[b] Doses are based on the subject's weight at screening; no dose adjustments will be made across the duration of study treatment.

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. All doses of LUM/IVA (morning and evening, as applicable) should be administered at approximately every 12 hours (± 2 hours) on each dosing occasion (e.g., if the morning dose is administered at 08:00 on Day 1, all subsequent morning doses should be administered between 06:00 and 10:00).
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 manual (e.g., apple sauce). Each dose (LUM 100 mg/IVA 125 mg or LUM 150 mg/IVA 188 mg) 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 Day 1 Visit, all subjects will be observed for 4 hours after the morning LUM/IVA dose.
4. The date, amount taken, and time of LUM/IVA administration, including whether food was taken with each dose, will be recorded for 1 day before PK sample collection and on the days of PK sample collection.
5. On days of scheduled visits (Day 1, Day 15, and during Weeks 4, 8, and 16), 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.
6. 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.
7. 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.
8. At the Week 24 Visit, the morning LUM/IVA dose will NOT be administered. The last LUM/IVA dose in Part B will be the evening dose administered the day before the Week 24 Visit.

10.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study with weight-based treatment. Randomization is not required in Part A or Part B.

10.4 Dose Modification for Toxicity

Part A and Part B

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

10.5 Packaging and Labeling

Part A and Part B

Vertex will supply the LUM/IVA granules in capsules in bottles for Part A and in stick packs in kits for Part B. 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.

10.6 Study Drug Supply, Storage, and Handling

Part A and Part B

Table 10-3 provides LUM/IVA 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, LUM/IVA will be accounted for as described in Section 10.7. Detailed instructions regarding the storage, handling, and dispensation of LUM/IVA will be provided in the pharmacy manual.

Table 10-3 Study Drug – Part A and Part B

Drug Name	Formulation/ Route	Packaging (Formulation Strength)		Storage Condition
LUM/IVA	Granules/ Oral	**Part A**: Supplied as 100-mg LUM/125-mg IVA granules in **1** capsule	**Part B**: 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	**Part A**: Supplied as 150-mg LUM/188-mg IVA granules in **2** capsules	**Part B**: 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)

IVA: ivacaftor; LUM: lumacaftor

10.7 Drug Accountability

Part A and Part B

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.

10.8 Disposal, Return, or Retention of Unused Drug

Part A and Part B

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.

10.9 Compliance

Part A and Part B

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.

10.10 Blinding and Unblinding

Part A and Part B

This is 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 (**Part A and Part B**, subjects ≥3 years of age at corresponding part's screening), sweat chloride (**Part B only**), and LCI results (**Part B only**, subjects ≥3 years of age at screening who consent/assent to the optional LCI Substudy) during the study, regardless if the subject permanently discontinues treatment.

11 ASSESSMENTS

11.1 Timing of Assessments

The timing of assessments is shown in:

- Table 3-1 and Table 3-2 for Part A, and
- Table 3-3 and Table 3-4 for Part B.

The following assessments must be performed in the order specified below when more than 1 assessment is required at a particular time point:

1. Predose ECGs and vital signs should be performed before any other procedures that may affect heart rate (e.g., blood draws including PK).
2. PK sampling and spirometry may be performed in either order.
3. For Part B only, the LCI assessment (if applicable) should be performed before spirometry.
4. For Part B only, the FE-1 sample may be collected at the study center during the study visit or may be collected by the subject up to 24 hours before the study visit at home and brought to the study visit. The sample may be collected pre- or postdose.

11.2 Subject and Disease Characteristics

Part A and Part B

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

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

11.3 Pharmacokinetics

11.3.1 Blood Sampling

Part A and Part B

For the evaluation of plasma concentrations of LUM, IVA, and their respective metabolites, PK blood samples will be collected from all subjects as noted in Table 3-2 (**Part A**) and Table 3-4 (**Part B**).

Samples from the PK sampling will be kept frozen by Vertex or its designee until all analyses have been completed and then disposed of according to Vertex or designee standard operating procedures.

The actual times may change upon agreement of the clinical pharmacologist and investigator, but the number of samples will remain the same (**Part A only**). All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Samples collected outside of the acceptable windows will be considered protocol deviations. For each PK blood draw, a record of LUM/IVA administration will be collected as described in Section 10.7. The collection date and time that each PK blood sample is drawn will also be recorded.
If appropriate, these samples may also be used for the evaluation of metabolites that arise during treatment, for further evaluation of the bioanalytical method, and/or for analyses that provide information on the metabolic pathways used by, or impacted by, LUM or IVA. These data will be used for exploratory purposes and may not be included in the clinical study report.

Details on sample collection, processing, and shipping will be provided in a separate guideline.

11.3.2 Processing and Handling of Pharmacokinetic Samples

Part A and Part B

Detailed procedures for the collection of blood samples and further procedures for processing and handling of samples for PK analysis will be provided in a separate guideline. The shipment address and assay laboratory contact information will be provided to the investigational site before initiation of the study.

11.3.3 Bioanalysis

Part A and Part B

Samples will be analyzed using a validated analytical method in compliance with Vertex or designee standard operating procedures. A description of the assay and validation data will be provided in separate reports.

11.4 Pharmacodynamics

Part A

Not applicable.

Part B

The PD assessments described in Section 11.4.1 through Section 11.4.9 will be performed in Part B.

11.4.1 Sweat Chloride

The sweat chloride test is a standard diagnostic tool for CF, serving as a biomarker of CFTR activity. Collection of sweat samples will be performed at visits specified in Table 3-3 and Table 3-4 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 must be conducted predose relative to the morning dose of LUM/IVA during the Treatment Period (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 regardless if the subject has prematurely discontinued treatment.

11.4.2 Lung Clearance Index

The optional LCI assessments derived from N_2-multiple-breath washout (MBW) testing will be conducted at visits specified in Table 3-3 and Table 3-4 to evaluate the effect of LUM/IVA on LCI and for evaluation of correlations between LCI and sweat chloride, and correlations between LCI and spirometry parameters. LCI will only be performed on subjects who are ≥3 years of age at Part B screening and who consent/assent to the optional LCI Substudy.

$LCI_{2.5}$ represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value, whereas $LCI_{5.0}$ represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value.[38]

Each MBW will be performed in multiple replicates for each visit and the final LCI value will be calculated from the technically acceptable washout replicates. The time for performing this test (in multiple replicates) during the study is approximately 1 hour at each study visit.

Pre-bronchodilator MBW testing is defined as MBW 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 MBW testing;
- withheld their long-acting bronchodilator (e.g., salmeterol) more than 12 hours before the MBW testing; and
- withheld their once-daily, long-acting bronchodilator (e.g., tiotropium bromide [Spiriva®]) for more than 24 hours before the MBW testing.

During the Screening Period, the MBW testing may be performed pre- or post-bronchodilator. At all other visits, all MBW testing should be performed "pre-bronchodilator." During the Treatment Period, MBW testing must be performed before dosing, unless noted otherwise. In the event that a subject forgets to withhold bronchodilator(s), MBW testing should be performed according to the following:

- If a subject's Day 1 MBW testing is pre-bronchodilator, but on a subsequent visit, the subject forgets to withhold bronchodilator use, post-bronchodilator MBW testing will be obtained for that visit only, and the visit will not be rescheduled.
- If on Day 1, the subject forgets to withhold his/her dose of bronchodilator, MBW testing should be performed post-bronchodilator and all subsequent MBW testing (according to the Schedule of Assessments detailed for LCI in Table 3-4) should be performed post-bronchodilator.
- Each MBW test will be recorded in the source documents as pre-bronchodilator or post-bronchodilator.

The MBW testing should be performed before the spirometry assessment (Section 11.6.7).

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 regardless if the subject has prematurely discontinued treatment.

11.4.3 Weight, Stature, and BMI

Refer to Section 11.6.4.

11.4.4 Other Events Related to Outcome

11.4.4.1 Antibiotic Therapy for Sinopulmonary Sign/Symptoms

New or changed antibiotic therapy (IV, inhaled, or oral) for the following sinopulmonary signs/symptoms will be determined and documented at visits as indicated in Table 3-3 and Table 3-4:

For this study, given the absence of a consensus definition for pulmonary exacerbation in clinical trials in this population, the definition appearing below will be applied to the signs and symptoms shown below for the analysis of pulmonary exacerbations.

Definition: New or changed treatment with oral, inhaled, or IV antibiotics **AND** fulfillment of 1 criterion from List A or 2 criteria from List B, within the period 3 days before antibiotic start date through antibiotic stop date.[39]

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

At visits indicated in Table 3-3 and Table 3-4, 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 time points noted in Table 3-4. Samples 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. Specific instructions for the collection, processing, and shipment of samples will be provided in a separate laboratory manual.

11.4.6 Immunoreactive Trypsinogen

Blood samples will be collected for IRT at the time points noted in Table 3-4. Specific instructions for the collection, processing, and shipment of samples will be provided in a separate laboratory manual.

11.4.7 Microbiology Cultures

At the time points noted in Table 3-4, a cotton-tipped swab will be used to collect the specimen from the posterior oropharyngeal wall and tonsillar pillars. Specific instructions for the collection, processing, and shipment of samples will be provided in a separate laboratory manual.

11.4.8 Spirometry

Refer to Section 11.6.7.

11.4.9 Acceptability/Palatability Assessment

At the time point noted in Table 3-4, the acceptability/palatability of LUM/IVA granules will be assessed by the investigator or authorized designee. The assessment will be conducted in 2 steps. First the acceptability/palatability of only the approved food/liquid will be assessed. Next, the acceptability/palatability of the approved food/liquid *with* the LUM/IVA granules mixed in will be assessed. All subjects will have their acceptance of the administrations and the volumes consumed recorded. The facial expressions of all subjects will also be observed and any spontaneous comments in regards to likes or dislikes will be noted. Immediately after receiving each administration (the approved food/liquid and the approved food/liquid *with* the LUM/IVA granules mixed in), subjects will be asked to rate acceptability/palatability using the visual analog scale that incorporates a 5-point facial hedonic scale.[40] All interviews will be conducted on a one-on-one basis in the clinic setting. Subjects will be familiarized with the scale using hypothetical situations before taste testing is conducted.

11.5 Efficacy

Part B Only

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

11.6 Safety

Part A and Part B

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

11.6.1 Adverse Events

Part A and Part B

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

Part A and Part B

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

Blood and urine samples for clinical laboratory assessments will be collected as shown in Table 3-1, Table 3-2, Table 3-3, and Table 3-4. Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

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

Table 11-1 Safety Laboratory Test Panels

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

[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.

Clinical laboratory assessments from screening will have no clinically significant findings that preclude participation in the study, as judged by the investigator, for a subject to receive LUM/IVA on Day 1.

CF genotype (**Screening Period only**): CF genotyping will be performed on all subjects to confirm the subject is homozygous for the *F508del-CFTR* mutation.

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

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

11.6.3 Elevation of Liver Function Test Parameters

Part A and Part B

It is strongly recommended that subjects with new ALT or AST elevations of ≥3 × ULN and clinical symptoms be followed closely, including repeat confirmatory testing performed by

the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT and AST levels, as clinically indicated.

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.

If no plausible 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, in consultation with the Vertex medical monitor or authorized designee. Subjects in whom treatment is discontinued for elevated transaminases should have their transaminases monitored closely until levels normalize or return to baseline.

Resumption of Study Drug

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

Mandatory Liver Function Testing

Liver function testing (ALT, AST, GGT, alkaline phosphatase, and total bilirubin) must be performed while subjects are receiving LUM/IVA treatment (see Table 3-2 and Table 3-4). These blood samples should be processed and shipped immediately per the laboratory manual.

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

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

11.6.4 Physical Examinations and Vital Signs

Part A and Part B

A PE of all body systems and vital signs assessment will be performed at screening and select study visits (see Table 3-1, Table 3-2, Table 3-3, and Table 3-4). At other visits, symptom-directed PEs and symptom-directed vital sign assessments can be performed at any time if triggered by AEs or if deemed necessary by the investigator or healthcare provider.

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

Vital signs include blood pressure (systolic and diastolic), temperature, 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. Weight and stature will be measured at the time points noted in Table 3-1, Table 3-2, Table 3-3, and Table 3-4. If children 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: BMI (kg/m^2) = body weight (kg) ÷ $stature^2$ (m^2).

Part B

An abbreviated PE will be performed according to the Schedule of Assessments (see Table 3-4).

The abbreviated PE will include an assessment of the following body systems: head/neck/thyroid, EENT, cardiovascular system, respiratory system, skin, and abdomen.

11.6.5 Electrocardiograms

Part A and Part B

Standard 12-lead ECGs will be performed using a machine with printout according to the Schedule of Assessments (see Table 3-1, Table 3-2, Table 3-3, and Table 3-4). 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.

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.

The PR, QT, and QT corrected for HR (QTc) intervals (including Fridericia's correction [$QTcF = QT/RR^{1/3}$]), QRS duration, and HR will be captured in the ECG database. The central ECG diagnostic service's standard reference ranges will be used throughout the study.

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 in whom treatment is discontinued for increased QTcF should have their QTcF monitored closely until it normalizes or returns to baseline.

11.6.6 Ophthalmologic Examination

Part A and Part B

In Part A, subjects will undergo an ophthalmologic examination at the Screening Visit (Table 3-1).

In Part B, subjects will undergo an ophthalmologic examination at the Screening Visit (Table 3-3) and at the Week 24 Visit OR the ETT Visit OR the Safety Follow-up Visit, as applicable (Table 3-4).

The ophthalmologic examination includes:

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

These examinations must be conducted by a licensed ophthalmologist. The Part A and Part B screening ophthalmologic examination must be completed and the results reviewed before enrollment. If cataract/lens opacity is identified and determined to be clinically significant by the licensed ophthalmologist at the screening examination, the subject must not be enrolled. The screening ophthalmologic examination does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the Screening Visit. Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination.

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 8.1.10. If the subject continues, more frequent ophthalmologic monitoring should be considered.

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

- history of steroid use
- history of trauma to the eye
- any family history of glaucoma, congenital cataracts, or cataracts arising later in life

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

11.6.7 Spirometry

Part A and Part B

Spirometry will be performed according to the American Thoracic Society Guidelines[41] at the time points noted in Table 3-1, Table 3-2, Table 3-3, and Table 3-4, according to the additional guidelines that follow. In Part A and Part B, spirometry will only be performed on subjects who are ≥3 years of age at screening of the corresponding part.

Pre-bronchodilator spirometry is defined as spirometry 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 spirometry assessment;
- withheld their long-acting bronchodilator (e.g., salmeterol) more than 12 hours before the spirometry assessment; and
- withheld their once-daily, long-acting bronchodilator (e.g., tiotropium bromide [Spiriva®]) for more than 24 hours before the spirometry assessment.

During the Screening Period, spirometry assessments may be performed pre- or post-bronchodilator. At all other visits, all spirometry assessments should be performed "pre-bronchodilator." During the Treatment Period, spirometry assessments must be

performed before dosing, unless noted otherwise. In the event that a subject forgets to withhold bronchodilator(s), spirometry should be performed according to the following:

- If a subject's Day 1 spirometry is pre-bronchodilator, but on a subsequent visit, the subject forgets to withhold bronchodilator use, a post-bronchodilator spirometry will be obtained for that visit only, and the visit will not be rescheduled.
- If on Day 1, the subject forgets to withhold his/her dose of bronchodilator, spirometry should be performed post-bronchodilator and all subsequent spirometric measurements (according to the Schedule of Assessments detailed in Table 3-2 and Table 3-4) should be performed post-bronchodilator.
- Each spirometry assessment will be recorded in the source documents as pre-bronchodilator or post-bronchodilator.

The parameters listed below will be normalized using the standards of GLI.[42]

- 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 regardless if the subject has prematurely discontinued treatment.

11.6.8 Contraception and Pregnancy

Not applicable.

12 STATISTICAL AND ANALYTICAL PLANS

Analysis of all data, including safety, PD and PK profiles, will be performed by Vertex or its designee. Two detailed analysis plans, 1 for the analysis of safety data in Part A, 1 for the analysis of safety and PD in Part B, will be presented in corresponding statistical analysis plans (SAPs), and a detailed analysis plan for PK profiles will be presented in a clinical pharmacology analysis plan (CPAP) before the data cut/lock for each part.

12.1 Sample Size and Power

Part A

No formal sample size calculations have been performed. The number of subjects participating is common in early clinical pharmacology studies and is considered sufficient to achieve the PK objectives of Part A.

Part B

No formal sample size calculations have been performed. The number of subjects in Part B is deemed adequate to meet the primary safety objective. Given approximately 56 subjects are planned for enrollment and assuming a 10% dropout rate, approximately 50 subjects will complete Part B. Table 12-1 displays estimates of the probability for observing AEs in at least 1 subject for the given incidence (θ) and sample size. With a total sample size of 50 subjects (completers), there is a 92.3% chance of observing AEs in at least 1 subject if the true incidence is 5%, and a 99.5% chance of observing AEs in at least 1 subject if the true incidence is 10%. The probabilities are the binomial probabilities calculated using S-PLUS ®.

Table 12-1 Probability of Observing Adverse Events in At Least 1 Subject if the Adverse Event Incidence (θ) is 5% and 10%

Sample Size	θ = 5%	θ = 10%
50[a]	92.3%	99.5%

[a] 50 reflects the sample size of the completers.

Additional subjects may be enrolled at the sponsor's discretion to achieve up to 30 subjects in the LCI Substudy. This sample size is consistent with prior exploratory studies conducting LCI assessments.[43,44]

12.2 Analysis Sets

Part A

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

Safety Set will include all subjects who received at least 1 dose of study drug in Part A. The safety analyses will be based on the Safety Set overall, unless otherwise specified. In addition, the summary by the dosing groups (LUM 100 mg/IVA 125 mg q12h and LUM 150 mg/IVA 188 mg q12h) at enrollment determined by weight at the Screening Visit will be provided as supplementary information.

Part B

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

Safety Set will include all subjects who received at least 1 dose of study drug in Part B. The safety analyses will be based on the Safety Set overall, unless otherwise specified. If the weight-based 2 doses are used in Part B, the summary by the dosing groups (LUM 100 mg/IVA 125 mg q12h and LUM 150 mg/IVA 188 mg q12h) at enrollment determined by weight at Screening Visit will be provided as supplementary information.

Full Analysis Set (FAS) will include all enrolled subjects in Part B who are exposed to any amount of study drug in Part B. PD analyses (except LCI) will be based on the FAS.

LCI Substudy Set will include all subjects who have signed informed consent (and assent, if applicable) to the optional LCI Substudy in Part B and enrolled and dosed in Part B. LCI-related analysis will be based on the LCI Substudy Set.

Subject data listings for both Part A and Part B will be the referenced using the All Subjects Set in the corresponding part, unless otherwise specified.

12.3 Statistical Analysis

This section presents a summary of the planned statistical analyses of safety for Part A and the planned statistical analysis of safety and PD for Part B. The Vertex Biometrics Department, or designee, will analyze the data derived from this study. 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 SAPs for the corresponding parts. Details of additional supportive safety (Part A and Part B), and PD (Part B only) analyses not included in the protocol will be provided in the SAPs. The SAPs will be finalized before the data cut/lock for each part.

12.3.1 General Considerations

This section applies to Part A and Part B, unless otherwise specified.

For Part A and Part B, all individual subject data based on All Subjects Set of the corresponding part will be presented in data listings.

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

Categorical variables will be summarized using counts and percentages.

Baseline value: For Part A and Part B, unless otherwise specified, the baseline value will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the initial administration of study drug.

- For ECG, the baseline will be defined as the average of the 3 pretreatment measurements on Day 1.

For Part B only:

- For LCI-related parameters, the values at each visit will be calculated from the technically acceptable washout replicates as detailed in Section 12.3.3.2.12. 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.
- For sweat chloride, the values at each visit will be based on the averaged measurements from left and right arms as specified in Section 12.3.3.2.1. The baseline will be defined as the average of the values at screening and the pretreatment measurement on Day 1. 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 postbaseline value - baseline value.

Relative change from baseline: will be calculated and presented in percentage as 100 × (postbaseline value - baseline value)/baseline value.

12.3.2 Background Characteristics

Unless otherwise specified, this section applies to both Parts A and B. All summaries will be based on the Safety Set of the corresponding part overall. For Part A, and Part B if the weight-based 2 doses are used, the summary by the dosing groups (LUM 100 mg/IVA 125 mg q12h and LUM 150 mg/IVA 188 mg q12h) at enrollment determined by weight at the Screening Visit will be provided as supplementary information, unless otherwise specified. No statistical hypothesis testing will be performed.

12.3.2.1 Subject Disposition

Number and percentage of subjects in the following categories will be summarized as appropriate.

Numbers of the following categories will be provided:

- All Subjects Set
- Dosed (Safety Set)
- Enrolled and dosed (FAS, Part B only)

Both numbers and percentages of subjects in the following categories will be provided. The percentage will be based on the number in Safety Set of the corresponding part.

- Completed study drug treatment
- Prematurely discontinued the treatment and the reasons for discontinuations
- Completed study
- Prematurely discontinued the study and the reasons for discontinuations

For Part B, similar disposition tables will be provided based on the LCI Substudy Set.

12.3.2.2 Demographics and Baseline Characteristics

Demographic, background (e.g., medical history), and baseline characteristics will be summarized. Important protocol deviations/violations will be provided as a subject data listing only. The rules used to define the important protocol deviations/violations will be provided in the SAPs.

The demographics, baseline characteristics, and medical history summary will be presented for the Safety Set of the corresponding part to allow review of the characteristics of those included in safety analyses, which will be based on this analysis set.

For Part B, similar tables for demographics and baseline characteristics will be provided based on the LCI Substudy Set.

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:** any medication that started before initial dosing of study drug in each part, regardless of when it ended.
- **Concomitant medication:** medication continued or newly received at or after initial dosing of study drug in each part to 14 days after the last dose of study drug in the corresponding part.
- **Post-treatment medication:** medication continued or newly received after 14 days after the last dose of study drug in each part.

A given medication can be classified as a prior medication, a concomitant medication, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment. If a medication has a missing or partially missing start/end date or time and it cannot be determined whether it was taken before initial dosing, concomitantly, or after 14 days after the last dose of study drug, it will be considered as prior, concomitant, and post-treatment.

Prior medications and concomitant medications will be summarized descriptively based on the Safety Set. Post-treatment medications will be listed for each subject.

12.3.2.4 Study Drug Exposure

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

Part A

Study drug exposure will be summarized overall based on Part A Safety Set. In addition, the summary by the dosing group (LUM 100 mg/IVA 125 mg q12h and LUM 150 mg/ IVA 188 mg q12h) at enrollment determined by weight at the Screening Visit will be provided as supplementary information.

Study drug exposure will be presented in an individual subject data listing to indicate whether the study drug was taken or not.

Part B

Duration of study drug exposure will be summarized overall based on Part B Safety Set and descriptively as a quantitative variable (number, mean, SD, SE, median, minimum, and maximum). If the weight-based 2 doses are used in Part B, summary by dosing groups (LUM 100 mg/IVA 125 mg q12h and LUM 150 mg/IVA 188 mg q12h) at enrollment determined by weight at the Screening Visit will be provided as supplementary information.

Additionally, the cumulative 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.

12.3.2.5 Study Drug Compliance

Part A

Compliance will be presented in an individual subject data listing.

Part B

Study drug compliance will be assessed by calculating as follows: 100 × (1 − [total number of days of study drug interruption] / [duration of study drug exposure + total number of days study drug interrupted after last dose, if any]). The total number of days of study drug interruption is defined as the sum of (number of days of each study drug interruption), where number of days of each study drug interruption is defined as the interruption end date − the corresponding interruption start date + 1.

Percent of stick packs taken will be calculated as follows: 100 × (total number of stick packs administered) / (2 × [duration of study drug exposure in days + total number of days study drug interrupted after last dose, if any]). Subjects who have a calculated percent of stick packs taken >100% will be considered as having taken 100% of stick packs.

Treatment compliance percentages and percent of stick packs taken will be summarized descriptively as quantitative variables (number, mean, SD, SE, median, minimum, and maximum). The number and percentage of subjects whose compliance is <80% or ≥80% and the number and percentage of subjects whose percent of stick packs taken is <80% or ≥80% will be summarized.

Study drug compliance will be based on Part B Safety Set overall. If the weight-based 2 doses are used in Part B, supplementary information will be provided for study drug compliance by the dosing group (LUM 100 mg/IVA 125 mg q12h and LUM 150 mg/IVA 188 mg q12h) at enrollment determined by weight at the Screening Visit.

12.3.3 Pharmacodynamics Analysis (Part B Only)

12.3.3.1 Analysis of Primary Endpoints

Not applicable.

12.3.3.2 Analysis of Secondary Pharmacodynamic Endpoints

Analyses for secondary PD endpoints are described in Sections 12.3.3.2.1 through 12.3.3.2.13. Analyses for other secondary endpoints and sensitivity analysis, supportive analysis, subgroup analysis of secondary variables, and analyses for other endpoints will be described in the SAP.

12.3.3.2.1 Absolute Change From Baseline in Sweat Chloride at Week 24

For each subject and at each time point, 2 sweat chloride measurements will be collected: 1 from the right arm and 1 from the left arm. Of the 2 measurements, only the sweat chloride value obtained from a sample volume ≥15 µL will be included in any analysis (i.e., values from samples with volumes <15 µL will be considered missing for analysis purposes). If a subject has replicated measurements at a postbaseline time point, then the median of the values will be used in data analyses. The sweat chloride results for the left and right arms will be averaged and used in the analysis if the sweat chloride values for the left and right arms are both ≥15 µL; if only 1 arm is ≥15 µL, then only that value will be used. Note: Any sweat chloride concentration values reported as <10 mmol/L or >160 mmol/L will be considered missing.

Descriptive summary statistics (n, mean, SD, SE, median, minimum, and maximum), along with the 95% confidence interval and within-group *P* value based on Normal approximation, will be provided for absolute change from baseline in sweat chloride at Week 24.

In addition, descriptive summary statistics, along with 95% confidence interval based on Normal approximation, will be provided for all other visits.

Additional analysis of the primary endpoint will be described in the SAP.

12.3.3.2.2 Absolute Change From Baseline in BMI/BMI-for-Age Z-score at Week 24

Descriptive summary statistics (n, mean, SD, SE, median, minimum, and maximum), along with the 95% confidence interval and within-group *P* value based on Normal approximation, will be provided for absolute change from baseline in BMI and BMI-for-age z-score at Week 24.
In addition, descriptive summary statistics, along with 95% confidence interval based on Normal approximation, will be provided at all other visits.

12.3.3.2.3 Absolute Change From Baseline in Weight/Weight-for-Age Z-Score at Week 24

Descriptive summary statistics (n, mean, SD, SE, median, minimum, and maximum), along with 95% confidence interval and within-group *P* values based on Normal approximation, will be provided for absolute change from baseline in weight and weight-for-age z-score at Week 24.

In addition, descriptive summary statistics, along with 95% confidence interval based on Normal approximation, will be provided at all other visits.

12.3.3.2.4 Absolute Change From Baseline in Stature/Stature-for-Age Z-score at Week 24

Descriptive summary statistics (n, mean, SD, SE, median, minimum, and maximum), along with 95% confidence interval and within-group *P* values based on Normal approximation, will be provided for absolute change from baseline in stature and stature-for-age z-score at Week 24.

In addition, descriptive summary statistics, along with 95% confidence interval based on Normal approximation, will be provided at all other visits.

12.3.3.2.5 Analysis of Pulmonary Exacerbation-related Other Secondary Pharmacodynamic Variables

- **Time-to-first pulmonary exacerbation through Week 24:** Time-to-first pulmonary exacerbation will be analyzed using Kaplan-Meier method. Cumulative incidence of pulmonary exacerbation will be summarized and plotted. Subjects without an exacerbation by Week 24 Visit will be censored at Week 24 Visit or at the last visit before the Safety Follow-up Visit for subjects with missing Week 24 Visit.
- **Number of pulmonary exacerbations through Week 24:** The number of pulmonary exacerbations through Week 24 [inclusive] (including both on-treatment events and events after treatment discontinuation), normalized by the time spent in the study (Week 24 date – first dose date +1), will be summarized.
- **Number of CF-related hospitalizations through Week 24:** For the number of CF-related hospitalizations through Week 24 [inclusive], the analysis will be similar to the analysis of the number of pulmonary exacerbations through Week 24.

12.3.3.2.6 Absolute Change in FE-1 Levels From Baseline at Week 24

Descriptive summary statistics (n, mean, SD, SE, median, minimum, and maximum), along with 95% confidence interval and within-group *P* values based on Normal approximation, will be provided for absolute change from baseline in FE-1 levels at Week 24. In addition, descriptive summary statistics, along with 95% confidence interval based on Normal approximation, will be provided at all other visits.

Number and percentage of subjects with pancreatic insufficiency, defined as having FE-1 level <200 μg/g, will be provided at Week 24 and at baseline. The within-group shift will be tested based on McNemar's test.

12.3.3.2.7 Absolute Change in Serum Levels of IRT From Baseline Through Week 24

For each subject, the serum levels of IRT through Week 24 for each subject will be derived as the simple arithmetic mean at each visit (Day 15, Weeks 4, 8, 16, and 24), regardless of on-treatment measurement or measurement after treatment discontinuation. As long as there is at least 1 measurement available, the average will be calculated based on all available measurements. If all measurements are missing, then the average through Week 24 will be missing and the subject will not be included in the summary for the average through Week 24. The absolute change in serum levels of IRT from baseline through Week 24 will be

derived similarly as the simple arithmetic mean of the absolute change in serum levels of IRT from baseline at each visit.

Summary statistics, along with 95% confidence interval and within-group *P* values based on Normal approximation, for absolute change from baseline in serum levels of IRT through Week 24 will be provided.

In additional, summary statistics, along with 95% confidence interval based on Normal approximation, will be provided at each visit.

12.3.3.2.8 Change in Microbiology Culture From Baseline at Week 24

Raw values and change in microbiology from baseline at Week 24 will be summarized descriptively. The summary will be separated for each possibly-detected organism.

12.3.3.2.9 Absolute Change From Baseline in ppFEV$_1$ at Week 24

Summary statistics, along with 95% confidence interval and within-group *P* values based on Normal approximation, for absolute change from baseline in ppFEV$_1$ will be provided at Week 24.

In addition, summary statistics, along with 95% confidence interval based on Normal approximation, will be provided at all other visits.

12.3.3.2.10 Absolute Change in Sweat Chloride From Week 24 at Week 26

Summary statistics, along with 95% CI and within-group *P* values based on Normal approximation, for absolute change from Week 24 will be provided at Week 26.

12.3.3.2.11 Acceptability/Palatability of LUM/IVA Granules at Day 1

Summary statistics will be provided for the acceptability/palatability data.

12.3.3.2.12 Absolute Change From Baseline in LCI$_{2.5}$ at Week 24

The LCI assessment at scheduled visits will be performed in multiple replicates. The LCI values at each visit included in the analysis will be the value calculated from the technically acceptable washout replicates.

When there is only one LCI value considered acceptable by the LCI central reader, the value will NOT be used. The assessment for that subject at the corresponding visit will be considered missing; when there are at least 2 LCI values considered acceptable by the LCI central reader, the arithmetic mean of the values from the accepted trials will be calculated as the value at the corresponding visit.

Descriptive summary statistics (n, mean, SD, SE, median, minimum, and maximum), along with 95% confidence interval and within-group *P* values based on Normal approximation, will be provided for absolute change from baseline in LCI$_{2.5}$ at Week 24.

In addition, descriptive summary statistics, along with 95% confidence interval based on Normal approximation, will be provided at all other visits.

12.3.3.2.13 Absolute Change From Baseline in $LCI_{5.0}$ at Week 24

Analysis of absolute change in $LCI_{5.0}$ from baseline at Week 24 will be similar to the analysis of absolute change in $LCI_{2.5}$ from baseline at Week 24.

12.3.4 Safety Analysis

Unless otherwise specified, this section applies to Part A and Part B.

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
- Ophthalmological examinations (Part B only)
- Spirometry (subjects ≥3 years age at screening)

For Parts A and B, safety endpoints will be analyzed based on the Safety Set for the corresponding part overall. For Part A, and Part B if the weight-based 2 doses are used, the summary by the dosing groups (LUM 100 mg/IVA 125 mg q12h and LUM 150 mg/ IVA 188 mg q12h) at each part's enrollment determined by weight at the Screening Visit will be provided as the supplementary information.

12.3.4.1 Adverse Events

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

- **Pretreatment AE**: any AE that started before initial dosing of study drug in each part.
- **TEAE**: any AE that increased in severity or that was newly developed during the Treatment Period which is defined as being the period from initial dosing of study drug in each part to 14 days after the last dose of study drug in the corresponding part.
- **Post-treatment AE**: any AE that increased in severity or that developed after 14 days after the last dose of study drug in each part.

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

For Part A and Part B, TEAE summaries will be presented using number and percentages of subjects.

An overview of TEAE profile will be provided, including total number of TEAEs, with number and percentage of subjects for the following categories: (1) All TEAEs, (2) Grades 3/4 TEAEs, (3) TEAEs by relationship to study drug, (4) TEAEs by maximum

severity, (5) TEAEs leading to treatment interruption, (6) TEAEs leading to treatment discontinuation, (7) Serious TEAEs, (8) Serious TEAEs related to study drug, and (9) TEAEs leading to death.

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

- All TEAEs
- Grades 3/4 TEAEs
- TEAEs by relationship to study drug
- TEAEs by maximum severity
- TEAEs leading to treatment interruption
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- Serious TEAEs related to study drug
- TEAEs leading to death
- Frequently reported TEAEs (Part B only)

Summaries will be presented by MedDRA system organ class (SOC) and preferred term (PT) using frequency counts and percentages. 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 that contain individual subject data for all TEAEs leading to treatment interruption, TEAEs leading to treatment discontinuation, deaths, and serious AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

12.3.4.2 Clinical Laboratory Assessments

For the laboratory measurements, the raw values and change from baseline values of the continuous hematology and chemistry results will be summarized in SI units at each scheduled time point. 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 will be summarized.

The number and percentage of subjects with at least 1 potentially clinically significant (PCS) event (i.e., categorical change) during the Treatment Period will be summarized. The PCS/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 baseline values will be provided at each scheduled time point 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 PCS ECG reading (i.e., categorical change) during the Treatment Period will be summarized. The PCS/categorical criteria will be provided in the SAP.

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

12.3.4.4 Vital Signs

For the vital signs measurements, the raw values and change from baseline values will be summarized at each scheduled time point: 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 PCS vital sign event (i.e., categorical change) during the Treatment Period will be summarized. The PCS/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 baseline values will be provided at each scheduled time point for the percent of oxygen saturation by pulse oximetry.

The number and percentage of subjects with shift changes from baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the Treatment Period will be provided.

12.3.4.6 Ophthalmological Examinations

Ophthalmological examination findings will be presented as a data listing for Part A (screening only) and Part B.

12.3.4.7 Spirometry

Spirometry data, including their raw values, absolute change from baseline and relative change from baseline, will be summarized descriptively at each visit.

12.3.4.8 Physical Examination

PE findings will be presented as a data listing only.

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 8.2) analysis will be provided in the IDMC Analysis Plan.

12.4 Clinical Pharmacology Analysis

12.4.1 Pharmacokinetic Analysis

Nonlinear mixed effects modeling will be applied for the PK analysis of LUM and IVA. Covariates (e.g., body weight) will be evaluated and included in the final population PK model if including them significantly improves the overall model fit and the accuracy and precision of population estimates of PK parameters.

Preliminary analysis will be performed on the PK data obtained from Part A of the current study. The PK analysis, along with safety and tolerability data from Part A, will be used to appropriately confirm the dose selection for Part B of the study (or adjust the doses if necessary before the start of Part B) based on PK parameters relative to historical results in the clinical development program. An interim PK analysis of data collected in Parts A and B may be performed to inform future development of LUM and IVA. This interim analysis, if performed, will not affect the conduct of the present study. Plasma concentrations for LUM, IVA, and their metabolites will be summarized using descriptive statistics by visits and time points.

12.4.2 Pharmacodynamic Analysis

12.4.3 Pharmacokinetic/Pharmacodynamic Analyses

The relationship between the outcome measures (e.g., sweat chloride) and drug concentrations may be used in exploratory analysis.

An interim PK/PD analysis of data collected in Part B (e.g., sweat chloride) may be performed to inform future development of LUM and IVA. This interim analysis, if performed, will not affect the conduct of the present study.

Details of methods used will be provided in the CPAP.

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 a serious adverse event (SAE). A Grade 4 laboratory value will be an SAE if the subject's clinical status indicates a life-threatening AE.

13.1.1.3 Documentation of Adverse Events

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

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit

- For enrolled subjects who do not have a Safety Follow-up Visit: through the end of study participation

All subject's caregivers 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 August 2015). 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. 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.

Table 13-4 Classifications for Outcome of an AE

Classification	Definition
Unknown	Outcome of an AE is not known (e.g., a subject lost to follow-up)

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

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

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

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

Clarification will be made between the terms "serious" and "severe" because they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event, as in mild, moderate, or severe myocardial infarction. The event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same

as “serious,” which is based on subject/event outcome or action described above, and is usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining expedited regulatory reporting obligations.

13.1.2.2 Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through the Safety Follow-up Visit, regardless of causality, will be reported by the investigator to Vertex GPS. In addition, all SAEs that occur after the Safety Follow-up Visit and are considered related to study drug 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 and possible etiologies. On the SAE Form, relationship to study drug 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 IRB/local IEC of all unexpected serious adverse drug reactions involving risk to human subjects.

13.2 Administrative Requirements

13.2.1 Ethical Considerations

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

13.2.2 Subject Information and Informed Consent

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

13.2.3 Investigator Compliance

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

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

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

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

13.2.6 Record Retention

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

13.2.7 Study Termination

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

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

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

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

13.3 Data Quality Assurance

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

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

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

13.4 Monitoring

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

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

13.5 Electronic Data Capture

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

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

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

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

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

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX15-809-115	Version #: 3.0	Version Date: 13APR2017
A Phase 3, 2-Part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Through 5 Years 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 #: VX15-809-115	Version #: 3.0	Version Date: 13APR2017
A Phase 3, 2-Part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation		

I have read Protocol VX15-809-115 Version 3.0, and agree to conduct the study according to its terms. I understand that all information concerning lumacaftor/ivacaftor and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date