1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3, Open-label, and Rollover Study to Evaluate the Long-term Safety and Tolerability of Lumacaftor/Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Homozygous for *F508del* and 12 to <24 Months of Age at Treatment Initiation

Vertex Study Number: VX19-809-124

IND Number: 79521

Date of Protocol: 12 February 2021 (Version 2.0)

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Summary of Changes to the Protocol

The previous version of this protocol (Version 1.0, 13 August 2019) was amended to create the current version (Version 2.0, 12 February 2021). The protocol history is below.

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.0, 13 August 2019	Original version
Version 2.0, 12 February 2021	Added the new dose of LUM 75 mg/IVA 94 mg and adjusted the lower weight bound for the LUM 100 mg/IVA 125 mg dose.

Key changes in the current version of the protocol are summarized below.

Change and Rationale	**Affected Sections**
Updated the planned dosing regimen based on PK results from Study 122 as follows: • Added a lower dose of LUM 75 mg/IVA 94 mg for subjects who weigh 7 to <9 kg at Day 1 for the Rollover Subjects and at screening for LUM/IVA-naïve subjects. • Updated the lower weight bound from 10 kg to 9 kg for the LUM 100 mg/IVA 125 mg dose The planned dosing regimen was also added to the study design figure.	Sections 2 (Figure 2-1), 9.1 (Figure 9-1), 9.6 (Table 9-2), and 10.3 (Table 10-1)
Added text to clarify the use of an assessment of Study 122B safety data before starting the enrollment of LUM/IVA-naïve subjects in each age group. Before initiating enrollment of LUM/IVA-naïve subjects 18 to <24 months of age, this safety assessment was performed in addition to meeting the minimum enrollment criteria in Study 122B.	Sections 2 (including Figure 2-1) and 9.1 (including Figure 9-1)
Removed footnote "c" from the "Follow-up OE" in the study design figure, as the footnote does not apply to the ophthalmologic examination.	Figure 2-1 and Figure 9-1
Added a ±30-minute window to the abbreviated physical examination performed postdose on Day 1 for the LUM/IVA-naïve subjects.	Table 3-2
Added a new section to describe the use of remote measures in extenuating circumstances, such as the COVID-19 pandemic.	Section 9.1.6; Table 3-1 and Table 3-2
Added clarification that screening sweat chloride results may be reviewed if needed to confirm eligibility.	Section 10.7
Removed the limitation that only central laboratory results for clinical laboratory assessments may be used for data analysis to allow for the use of local laboratories in extenuating circumstances, as described in new Section 9.1.6.	Section 11.4.2
Updated the analysis definitions for "Prior Medication" and "Pretreatment Adverse Event (AE)" to capture medications taken and AEs during Study 122 for the Rollover subjects.	Sections 12.3.2.3 and 12.3.5.1

Typographical and administrative changes were also made to improve the clarity of the document.

2 PROTOCOL SYNOPSIS

Title A Phase 3, Open-label, and Rollover Study to Evaluate the Long-term Safety and Tolerability of Lumacaftor/Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Homozygous for *F508del* and 12 to <24 Months of Age at Treatment Initiation

Brief Title Long-term Safety of Lumacaftor/Ivacaftor in Subjects With Cystic Fibrosis Who Are Homozygous for *F508del* and 12 to <24 Months of Age at Treatment Initiation

Clinical Phase and Clinical Study Type Phase 3, safety

Objectives

Primary Objective

To evaluate the safety and tolerability of long-term lumacaftor/ivacaftor (LUM/IVA) treatment in subjects with cystic fibrosis (CF), who are homozygous for *F508del* and 12 to <24 months of age at treatment initiation

Secondary Objective

To evaluate the pharmacodynamics (PD) of long-term LUM/IVA treatment in subjects with CF, who are homozygous for *F508del* and 12 to <24 months of age at treatment initiation

Endpoints

Primary Endpoint

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

Secondary Endpoint

Absolute change from baseline in sweat chloride

Exploratory Endpoints

- Absolute change from baseline in the following growth parameters:
  - Body mass index (BMI)-for-age z-score and BMI
  - Weight-for-age z-score and weight
  - Length/height-for-age z-score and length/height
  - Weight-for-length z-score
- Absolute change from baseline in the following markers of pancreatic function:
  - Fecal elastase-1 (FE-1) levels
  - Serum immunoreactive trypsin and trypsinogen (IRT) levels
- Absolute change from baseline in fecal calprotectin, a marker of intestinal inflammation

Number of Subjects Approximately 50 subjects

Study Population Male and female subjects with CF, homozygous for *F508del,* and who are 12 to <24 months of age at LUM/IVA treatment initiation

Rollover Subjects: Subjects who completed LUM/IVA treatment and the Safety Follow-up Visit in Study VX16-809-122 Part B (Study 122B)

LUM/IVA-naïve Subjects: Subjects who did not participate in in Study 122B and are 12 to <24 months of age at Study 124 Day 1.

Investigational Drug

Active substance: LUM/IVA fixed-dose combination

Activity: CFTR corrector and potentiator

Strength and route of administration:

- LUM 75-mg/IVA 94-mg granules for oral administration
- LUM 100-mg/IVA 125-mg granules for oral administration
- LUM 150-mg/IVA 188-mg granules for oral administration

Study Duration

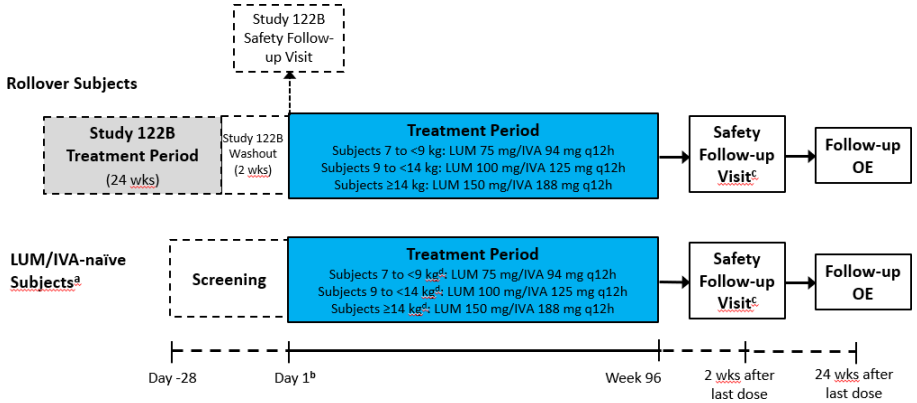
Rollover Subjects: The total duration is up to 120 weeks (96 weeks for the Treatment Period and 24 weeks for the Follow-up OE)

LUM/IVA-naïve Subjects: The total duration is up to 124 weeks (up to 28 days for the Screening Period, 96 weeks for the Treatment Period, and 24 weeks for the Follow-up OE)

Study Design

This is a Phase 3, multicenter, open-label study in subjects who are 12 to <24 months of age at initiation of LUM/IVA treatment (Figure 2-1).

Figure 2-1 Study 124 Design



IVA: ivacaftor; LUM: lumacaftor; OE: ophthalmological examination; q12h: every 12 hours; wks: weeks

[a] LUM/IVA-naïve subjects (by age group: 18 to <24 months and 12 to <18 months) will be able to enroll in Study 124 once minimum enrollment has been met in Study 122B (n = 10 subjects in each age group), and after an assessment of safety data from Study 122B through Week 12 for ≥5 subjects in each age group.

[b] For Rollover Subjects, the Day 1 Visit should be the same day as the Safety Follow-up Visit in Study 122B.

[c] The Safety Follow-up Visit will not be required for subjects transitioning to commercial LUM/IVA.

[d] For LUM/IVA-naïve subjects, doses will be determined by weight at screening.

The subjects enrolled in this study include:

Rollover Subjects: Subjects who participated in Study 122B and completed the Study 122B Safety Follow-up Visit.

LUM/IVA-naïve Subjects: Subjects who did not participate in Study 122B and are 12 to <24 months of age at Study 124 Day 1. These subjects will enroll by age group as follows:

- Subjects who are 18 to <24 months of age can enroll in Study 124 after a minimum of 10 subjects (aged 18 to <24 months) have enrolled in Study 122B, and after an assessment of safety data from Study 122B through Week 12 for ≥5 subjects aged 18 to <24 months.
- Subjects who are 12 to <18 months of age can enroll in Study 124 after a minimum of 10 subjects (aged 12 to <18 months) have enrolled in Study 122B, and after an assessment of safety data from Study 122B through Week 12 for ≥5 subjects aged 12 to <18 months.

Note: Subjects who are 18 to <24 months of age will start enrolling in Study 124 before any subjects who are 12 to <18 months of age enroll as a result of the study design in Study 122, which includes sequential age cohorts.

Rollover and LUM/IVA-naïve subjects will receive LUM/IVA every 12 hours (q12h), according to a weight-based dosing regimen determined in Study 122, for up to 96 weeks.

Dose(s) and/or weight bounds may be adjusted after review of safety, tolerability, available pharmacokinetic (PK) data from Study 122, as well as any updated modeling approaches resulting from such data. Changes to study drug dose(s) and/or weight bounds will be communicated to site personnel through a memorandum entitled "Justification for Dose Selection" to ensure clarity and consistency in study conduct.

During the treatment period, doses may also be adjusted upward based on consistent weight gain; however, no downward dose adjustments will be made if a subject's weight decreases.

Assessments

Safety: AEs, clinical laboratory (serum chemistry and hematology), standard 12-lead ECGs, vital signs, pulse oximetry, physical examinations, and OEs

Pharmacodynamic: Sweat chloride

Exploratory: BMI, BMI-for-age z-score, weight, weight-for-age z-score, length/height, length/height-for-age z-score, weight-for-length-for-age z-score, FE-1, IRT, and fecal calprotectin

Statistical Analyses

No formal sample size calculations have been performed. The study will enroll approximately 50 subjects to provide data for the assessment of long-term safety in the target patient population, as requested by a regulatory agency.

Data from all safety, pharmacodynamic (PD), and exploratory endpoints will be analyzed using descriptive statistics. Raw and change from baseline values will be summarized descriptively for the continuous endpoints; number of subjects and percentages will be summarized for the categorical endpoints.

IDMC Reviews

Data will be reviewed by an independent data monitoring committee (IDMC) to ensure the safety of the subjects in the study. Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be included in the IDMC charter, which will be finalized before the first subject is enrolled.

3 SCHEDULE OF ASSESSMENTS

Schedules of assessments are in Table 3-1 and Table 3-2.

Table 3-1 Study VX19-809-124: Rollover Subjects

Event/ Assessment[a]	Treatment Period (Day 1 Through Week 96)					ETT Visit[b]	SFU Visit [c]	Follow-up OE	Comments
	Day 1[d]	Day 3 (± 1 Day)	Day 15 (± 3 Days)	Weeks 12, 24, 36, 48, 60, 72, and 84 (± 7 Days)	Week 96 (± 7 Days)	As Soon As Possible After Last Dose	2 Weeks (± 4 Days) After Last Dose	24 Weeks (± 14 Days) After Last Dose	
Informed consent	X								
Inclusion/exclusion criteria confirmation	X								
Telephone contact		X							Assessment of subject's status, any AEs, concomitant medications, treatments, and procedures.
Clinic visit	X		X	X	X	X	X		See Section 9.1.6 for use of remote measures in extenuating circumstances.
Length/height and weight	X		X	X	X	X	X		Measured with the subject in a dry diaper or dry underclothes. If the subject is >2 years of age and can stand unassisted and follow directions, standing height should be measured; otherwise recumbent length should be measured. (Section 11.3.1).
Vital signs	X		X	X	X	X	X		The subject should rest for at least 5 minutes, if possible, before having vital signs measured. (Section 11.4.4)
Pulse oximetry	X		X	X	X	X	X		The subject should rest for at least 5 minutes, if possible, before having pulse oximetry measured. (Section 11.4.4)

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

[b] If the ETT Visit occurs ≥10 days after the last dose of LUM/IVA, SFU Visit will not be required (Section 9.1.4). Subjects who prematurely discontinue LUM/IVA treatment for AEs should be followed until the AE is considered resolved.

[c] The SFU Visit is required for 1) subjects who complete their ETT Visit <10 days after the last dose of LUM/IVA (footnote b and Section 9.1.4); and 2) subjects who interrupt LUM/IVA treatment and complete their Week 96 Visit <10 days after the last dose of LUM/IVA; it is not required for subjects who continue onto commercially available, physician-prescribed LUM/IVA within 2 weeks (± 4 days) of completing LUM/IVA treatment at the Week 96 or ETT Visit.

[d] For subjects at sites activated by the time of their Study 122B SFU Visit, their Study 124 Day 1 Visit will be on the **same day** as their Study 122B SFU Visit, and any Study 124 Day 1 assessments that were specified to be performed at the Study 122B SFU Visit do not need to be repeated. If the Study 124 Day 1 Visit **does not coincide** with the subject's Study 122B SFU Visit, and if Study 124 Day 1 is ≤9 days after the Study 122B SFU Visit, the Study 124 Day 1 assessments do not need to be repeated. If Study 124 Day 1 is >9 days after the Study 122B SFU Visit, the subject will complete all Study 124 Day 1 assessments (except the OE if it was performed ≤12 weeks before the Study 124 Day 1 Visit). See Section 9.1 for details.

Table 3-1 Study VX19-809-124: Rollover Subjects

Event/ Assessment[a]	Treatment Period (Day 1 Through Week 96)					ETT Visit[b]	SFU Visit [c]	Follow-up OE	Comments
	Day 1[d]	Day 3 (± 1 Day)	Day 15 (± 3 Days)	Weeks 12, 24, 36, 48, 60, 72, and 84 (± 7 Days)	Week 96 (± 7 Days)	As Soon As Possible After Last Dose	2 Weeks (± 4 Days) After Last Dose	24 Weeks (± 14 Days) After Last Dose	
Ophthalmological examination	X			Weeks 24, 48, 72	X	X[e]		X	To be performed by a licensed ophthalmologist, preferably a pediatric ophthalmologist. May be completed ± 2 weeks of the scheduled visit. (Section 11.4.6)
Physical examination	X			X	X	X	X		Section 11.4.4
12-lead ECGs	X			Weeks 24, 48	X	X	X		The subject should rest for at least 5 minutes, if possible, before having ECGs measured. To be performed before any other procedures that may affect heart rate, such as blood draws. (Section 11.4.5)
Serum chemistry and hematology	X		X (LFTs only)	X	X	X	X		Section 11.4.2
IRT	X			X	X	X	X		Section 11.3.2.2
Sweat chloride	X			Weeks 24, 48	X	X			At each time point, 2 samples will be collected, 1 sample from each arm (left and right) (Section 11.2.1).
Fecal sample collection	X			Weeks 24, 48	X	X			May be collected during the clinic visit or by the subject's caregiver up to 48 hours before the clinic visit and brought to the clinic visit (Section 11.3.2.1).
LUM/IVA dosing	**LUM/IVA q12h**								Administered q12h (± 2 hours) within 30 minutes of consuming fat-containing food according to the guidelines in Section 9.6. The last dose will be the previous dose (e.g., evening dose) administered before the Week 96 Visit. See Section 9.6 for dose determination details.
Study drug count			X	X	X	X			
Medications, treatments, and procedures review	Continuous from signing of ICF through the SFU Visit								Section 9.5
AEs	Continuous from signing ICF through the SFU Visit							*Ocular AEs only*	Section 11.4.1

AE: adverse event; ETT: Early Termination of Treatment; ICF: informed consent form; IRT: immunoreactive trypsinogen and trypsin; IVA: ivacaftor; LFT: liver function test; LUM: lumacaftor; OE: ophthalmological examination; q12h: every 12 hours; SFU: Safety Follow-up

[e] The OE for the ETT Visit will be conducted for all subjects who prematurely discontinue LUM/IVA dosing (for any reason) unless performed in the 12 weeks before the ETT Visit.

Table 3-2 Study VX19-809-124: LUM/IVA-naïve Subjects

Event/Assessment[a]	Screening	Treatment Period (Day 1 Through Week 96)							ETT Visit[b]	SFU Visit[c]	Follow-up OE	Comments
	Days -28 Through -1	Day 1	Day 3 (± 1 Day)	Day 15 (± 3 Days)	Weeks 4, 8, 12, and 16 (± 5 Days)	Week 20 (± 5 Days)	Weeks 24, 36, 48, 60, 72, and 84 (± 7 Days)	Week 96 (± 7 Days)	As Soon As Possible After Last Dose	2 Weeks (± 4 Days) After Last Dose	24 Weeks (± 14 Days) After Last Dose	
Informed consent	X											
Inclusion/exclusion criteria confirmation	X											
Clinic visit	X	X		X	X		X	X	X	X		See Section 9.1.6for use of remote measures in extenuating circumstances.
Telephone contact			X			X						Assessment of subject's status, any AEs, concomitant medications, treatments, and procedures.
Demographics	X											
Medical history	X											
CFTR genotype	X											Retesting is not required for subjects who have acceptable documentation of a genotype test as described in Section 11.4.2.
Length/height and weight	X	X		X	X		X	X	X	X		Measured with the subject in a dry diaper or dry underclothes. If the subject is >2 years of age and can stand unassisted and follow directions, standing height should be measured; otherwise recumbent length should be measured. (Section 11.3.1).
Vital signs	X	X		X	X		X	X	X	X		The subject should rest for at least 5 minutes, if possible, before having vital signs measured. **Days 1 and 15**: Predose and 1 to 2 hours and 4 to 6 hours postdose (Section 11.4.4)
Pulse oximetry	X	X		X	X		X	X	X	X		The subject should rest for at least 5 minutes, if possible, before having pulse oximetry measured.

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

[b] If the ETT Visit occurs ≥10 days after the last dose of LUM/IVA, the SFU Visit will not be required (Section 9.1.3). Subjects who prematurely discontinue LUM/IVA treatment for AEs should be followed until the AE is considered resolved.

[c] The SFU Visit is required for 1) subjects who complete their ETT Visit <10 days after the last dose of LUM/IVA (footnote b and Section 9.1.4); and 2) subjects who interrupt LUM/IVA treatment and complete their Week 96 Visit <10 days after the last dose of LUM/IVA; it is not required for subjects who continue onto commercially available, physician-prescribed LUM/IVA within 2 weeks (± 4 days) of completing LUM/IVA treatment at the Week 96 or ETT Visit.

Table 3-2 Study VX19-809-124: LUM/IVA-naïve Subjects

Event/Assessment[a]	Screening	Treatment Period (Day 1 Through Week 96)							ETT Visit[b]	SFU Visit[c]	Follow-up OE	Comments
	Days -28 Through -1	Day 1	Day 3 (± 1 Day)	Day 15 (± 3 Days)	Weeks 4, 8, 12, and 16 (± 5 Days)	Week 20 (± 5 Days)	Weeks 24, 36, 48, 60, 72, and 84 (± 7 Days)	Week 96 (± 7 Days)	As Soon As Possible After Last Dose	2 Weeks (± 4 Days) After Last Dose	24 Weeks (± 14 Days) After Last Dose	
												Days 1 and 15: Predose and 1 to 2 hours and 4 to 6 hours postdose (Section 11.4.4)
Ophthalmological examination	X						Weeks 24, 48, 72	X	X[d]		X	To be performed by a licensed ophthalmologist, preferably a pediatric ophthalmologist. May be completed ± 2 weeks of the scheduled visit. (Section 11.4.6)
Physical examination (PE)	X	X		Abbrev	Week 12		X	X	X	X		**Day 1:** Full PE predose and an abbreviated PE 4 hours (±30 minutes) postdose (Section 11.4.4).
Standard 12-lead ECG	X				Weeks 4, 12		Weeks 24, 48	X	X	X		The subject should rest for at least 5 minutes, if possible, before having ECGs measured. To be performed before any other procedures that may affect heart rate, such as blood draws. (Section 11.4.5)
Serum chemistry and hematology	X	X		X (LFTs only)	X		X	X	X	X		If the screening blood draw for chemistry and hematology was collected ≤9 days before Day 1, then a Day 1 blood sample does not need to be collected. **Weeks 4 and 12:** Serum chemistry and hematology are collected **Day 15, Weeks 8 and 16**: LFTs only (Sections 11.4.2 and 11.4.3)
IRT	X				Weeks 4, 12		X	X	X	X		Section 11.3.2.2
Sweat chloride	X	X			Weeks 4, 12		Weeks 24, 48	X	X			Day 1 test is not required for subjects who have a valid sweat sample at screening. At each time point, 2 samples will be collected, 1 sample from each arm (left and right) (Section 11.2.1).

[d] The OE for the ETT Visit will be conducted for all subjects who prematurely discontinue LUM/IVA dosing (for any reason) unless performed in the 12 weeks before the ETT Visit.

Table 3-2 Study VX19-809-124: LUM/IVA-naïve Subjects

Event/Assessment[a]	Screening	Treatment Period (Day 1 Through Week 96)							ETT Visit[b]	SFU Visit[c]	Follow-up OE	Comments
	Days -28 Through -1	Day 1	Day 3 (± 1 Day)	Day 15 (± 3 Days)	Weeks 4, 8, 12, and 16 (± 5 Days)	Week 20 (± 5 Days)	Weeks 24, 36, 48, 60, 72, and 84 (± 7 Days)	Week 96 (± 7 Days)	As Soon As Possible After Last Dose	2 Weeks (± 4 Days) After Last Dose	24 Weeks (± 14 Days) After Last Dose	
Fecal sample collection	X				Weeks 4, 12		Weeks 24, 48	X	X			Sample collected before first dose of study drug may be collected **either** at screening **OR** up to 48 hours before the Day 1 Visit. All other samples may be collected during the clinic visit or by the subject's caregiver up to 48 hours before the clinic visit and brought to the clinic visit (Section 11.3.2.1).
LUM/IVA dosing		**LUM/IVA q12h**										Administered q12h (± 2 hours) within 30 minutes of consuming fat-containing food according to the guidelines in Section 9.6. The last dose will be the previous dose (e.g., evening dose) administered before the Week 96 Visit. See Section 9.6 for dose determination details.
Observation 4 hours after the first dose		X										
Study drug count				X	X		X	X	X			
Medications, treatments, and procedures review	Continuous from signing of ICF through the SFU Visit											Section 9.5
AEs	Continuous from signing of ICF through the SFU Visit										*Ocular AEs only*	Section 11.4.1

Abbrev: abbreviated; AE: adverse event; BMI: body mass index; CF: cystic fibrosis; *CFTR*: CF transmembrane conductance regulator gene; ETT: Early Termination of Treatment; ICF: informed consent form; IRT: immunoreactive trypsin and trypsinogen; IVA: ivacaftor; LFT: liver function test; LUM: lumacaftor; OE: ophthalmological examination; PE: physical examination; q12h: every 12 hours; SFU: Safety Follow-up

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BMI	body mass index
CF	cystic fibrosis
CFTR	CF transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
CI	confidence interval
Cl^-	chloride ion
CPAP	clinical pharmacology analysis plan
CRF	case report form
CYP	cytochrome P450
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
eGFR	estimated glomerular filtration rate
ETT	Early Termination of Treatment
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F508del	CFTR protein lacking the phenylalanine normally found at position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FE-1	fecal elastase-1
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GPP3	Good Publication Practices
GPS	Global Patient Safety
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IDMC	independent data monitoring committee
IEC	independent ethics committee
IRB	institutional review board
IRT	immunoreactive trypsinogen
IV	intravenous
IVA	ivacaftor
LFT	liver function test
LLN	lower limit of normal

Abbreviation	Definition
LUM	lumacaftor
MedDRA	Medical Dictionary for Regulatory Activities
OE	ophthalmological examination
PC	publication committee
PD	pharmacodynamics, pharmacodynamics
PERT	pancreatic enzyme replacement therapy
PEx	pulmonary exacerbation
PK	pharmacokinetic, pharmacokinetics
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PR	PR interval, segment
PT	Preferred Term
q12h	every 12 hours
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SC	steering committee
SD	standard deviation
SE	standard error
SFU	Safety Follow-up
SI	SI units (International System of Units)
SOC	System Organ Class
SUSAR	suspected, unexpected, serious adverse reaction
TE	treatment-emergent
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WHO-DD	World Health Organization-Drug Dictionary

Definitions of Terms

Abbreviated study numbers: In the body of the text, study numbers are abbreviated to the last 3 digits and the study part letter (if applicable) for lumacaftor/ivacaftor studies (e.g., Study VX16-809-122 Part B is Study 122B).

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 is caused by a defect in the gene encoding CFTR, an epithelial chloride ion channel that is responsible for aiding in the regulation of salt and water absorption and secretion in various tissues.[1] This function is abnormal in patients with CF due to a loss of cell surface expression and/or function of CFTR. CF affects more than 78,000 individuals worldwide.[2, 3] 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.[4, 5] Although the disease affects multiple organs, progressive loss of lung function is the leading cause of mortality.[6]

Approximately half of the total CF patient population is <18 years of age.[2, 3, 7, 8] In the US, 58.4% of all new diagnoses are detected by newborn screening.[2] Early diagnosis has been associated with better outcomes later in life.[9] Pancreatic destruction leading to pancreatic exocrine insufficiency begins in utero, with over 90% of homozygous F508del infants demonstrating pancreatic insufficiency requiring pancreatic enzyme replacement therapy (PERT). Lung involvement is primarily manifested by changes in airway surface liquid height leading to impaired mucociliary clearance and subsequent neutrophilic airway inflammation, bacterial colonization, and infection leading to structural lung damage that begins shortly after birth.[10, 11]

CFTR modulators, such as lumacaftor (LUM; VX-809)/ivacaftor (IVA; VX-770) combination therapy (Orkambi™), target the underlying cause of CF and have the potential to alter the course of the disease. LUM/IVA 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 is designed to support the hypothesis that an oral chronic treatment restoring CFTR function can lead to improved pulmonary and extrapulmonary manifestations of CF, prevent progressive lung damage, and ultimately prolong survival.

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

5.2 Study Rationale

The primary objectives of Study VX16-809-122 (Study 122) are to obtain pharmacokinetic (PK) and safety information to support a proposed indication expansion of LUM/IVA in subjects 12 to <24 months of age with CF, homozygous for *F508del*. The primary objective of Study VX19-809-124 (Study 124, the current study) is to evaluate the long-term safety of LUM/IVA in subjects 12 to <24 months of age with CF, homozygous for *F508del*, at the time of treatment initiation.

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the safety and tolerability of long-term LUM/IVA treatment in subjects with CF, who are homozygous for *F508del* and 12 to <24 months of age at treatment initiation

6.2 Secondary Objective

To evaluate the pharmacodynamics (PD) of long-term LUM/IVA treatment in subjects with CF, who are homozygous for *F508del* and 12 to <24 months of age at treatment initiation

7 STUDY ENDPOINTS

7.1 Primary Endpoint

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

7.2 Secondary Endpoint

Absolute change from baseline in sweat chloride

7.3 Exploratory Endpoints

- Absolute change from baseline in the following growth parameters:
  - Body mass index (BMI)-for-age z-score and BMI
  - Weight-for-age z-score and weight
  - Length/height-for-age z-score and length/height
  - Weight-for-length z-score
- Absolute change from baseline in the following markers of pancreatic function:
  - Fecal elastase-1 (FE-1) levels
  - Serum immunoreactive trypsin and trypsinogen (IRT) levels
- Absolute change from baseline in fecal calprotectin, a marker of intestinal inflammation

8 STUDY POPULATION

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

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

8.1 Rollover Subjects

8.1.1 Inclusion Criteria

1. Subject's legally appointed and authorized representative (e.g., parent or legal guardian) will sign and date an informed consent form (ICF).
2. Completed the 24-week Treatment Period and the Safety Follow-up Visit in Study 122B.

   Note: Subjects who had study drug interruptions during Study 122B are eligible for Study 124 if they completed the study visits in the Treatment Period and the Safety Follow-up Visit. Subjects who had a study drug interruption at Week 24 of Study 122B or subjects who resumed study drug in Study 122B after a study drug interruption due to elevated transaminases but who did not complete at least 4 weeks of rechallenge with study drug (due

to <4 weeks remaining in the Study 122B Treatment Period) must meet eligibility criteria and receive approval from the Vertex medical monitor.

3. Subject's legally appointed and authorized representative (e.g., parent or legal guardian) are willing to have the subject remain on a stable CF medication regimen through the Safety Follow-up Visit.

8.1.2 Exclusion Criteria

1. Prematurely discontinued LUM/IVA treatment in Study 122B.
2. History of any comorbidity or laboratory abnormality that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering LUM/IVA to the subject (e.g., cirrhosis with portal hypertension).
3. History of drug intolerance or other serious reactions to LUM/IVA in Study 122B that would pose an additional risk to the subject in the opinion of investigator and which should be discussed with the Vertex medical monitor.
4. Subjects with a history of allergy or hypersensitivity to LUM/IVA.
5. Liver function test (LFT) abnormality meeting criteria for LUM/IVA treatment interruption at the completion of Study 122B, for which no convincing alternative etiology is identified.
6. QTc value at the completion of Study 122B that would pose an additional risk to the subject in the opinion of investigator, and should be discussed with the Vertex medical monitor (e.g., remained above the threshold value [>45 msec from baseline or >500 msec] on repeated measurement or was noted on 2 or more occasions with no identified alternative etiology for the increased QTc).
7. History of poor compliance with LUM/IVA and/or procedures in Study 122B as deemed by the investigator.
8. Participation in an investigational drug study (including studies investigating LUM and/or IVA) other than Study 122B. NOTE: Participation in a non-interventional study is permitted (including observational studies, registry studies, and studies requiring blood collections without administration of study drug).

8.2 LUM/IVA-naïve Subjects

8.2.1 Inclusion Criteria

1. Subject's legally appointed and authorized representative (e.g., parent or legal guardian) will sign and date an informed consent form (ICF).
2. As deemed by the investigator, the subject's legally appointed and authorized representative (e.g., parent or legal guardian) must be able to understand protocol requirements, restrictions, and instructions. The subject's legally appointed and authorized representative should be able to ensure that the subject will comply with, and is likely to complete, the study as planned.
3. Subjects (male and female) will be 12 to <24 months of age on Day 1.
4. Weight at screening must be within the weight limits as defined for the study drug dose levels (see Section 9.6) or according to the dosing guidelines identified in the "Justification for Dose Selection" memorandum effective at the time a subject is screened.

5. Subjects with confirmed diagnosis of CF[12] at screening. CF is defined as:
   - 2 CF-causing mutations (all as documented in the subject's medical record)
     - Subjects must be homozygous for *F508del* (genotype to be confirmed at screening): If a genotype test has been performed previously and is documented in the subject's medical record, the subject is not required to be tested for *CFTR* genotype at screening, but the subject's eligibility must be approved by the Vertex medical monitor. If a historic genotype result is not available at screening or if the historic genotype result is not approved by the Vertex medical monitor, the subject will be tested for *CFTR* genotype at screening, and the results must be reviewed before the first dose. Note: Newborn screening genotype results are not sufficient for eligibility.

   AND (1 of the 2 criteria below)

   - chronic sinopulmonary disease OR gastrointestinal/nutritional abnormalities

     OR

   - 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 screening. If an eligible historical sweat chloride result is documented in the subject's medical record, that result alone (and not the screening result) may be used to determine eligibility.
6. Subjects with stable CF disease as deemed by the investigator at screening.
7. Subject's legally appointed and authorized representative (e.g., parent or legal guardian) are willing to have the subject remain on a stable CF medication regimen through the Safety Follow-up Visit.

8.2.2 Exclusion Criteria

1. History of any comorbidity reviewed at screening 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 screening 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 screening:
   - Hemoglobin <9.5 g/dL
   - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin >2 × upper limit of normal (ULN)
   - Chronic kidney disease of Stage 3 (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 calculated by the Bedside Schwartz equation[13]) based on the normal range for eGFR in this age group (62 to 191)
4. An acute upper or lower respiratory infection, pulmonary exacerbation (PEx), 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 screening. 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 screening.
   - 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.

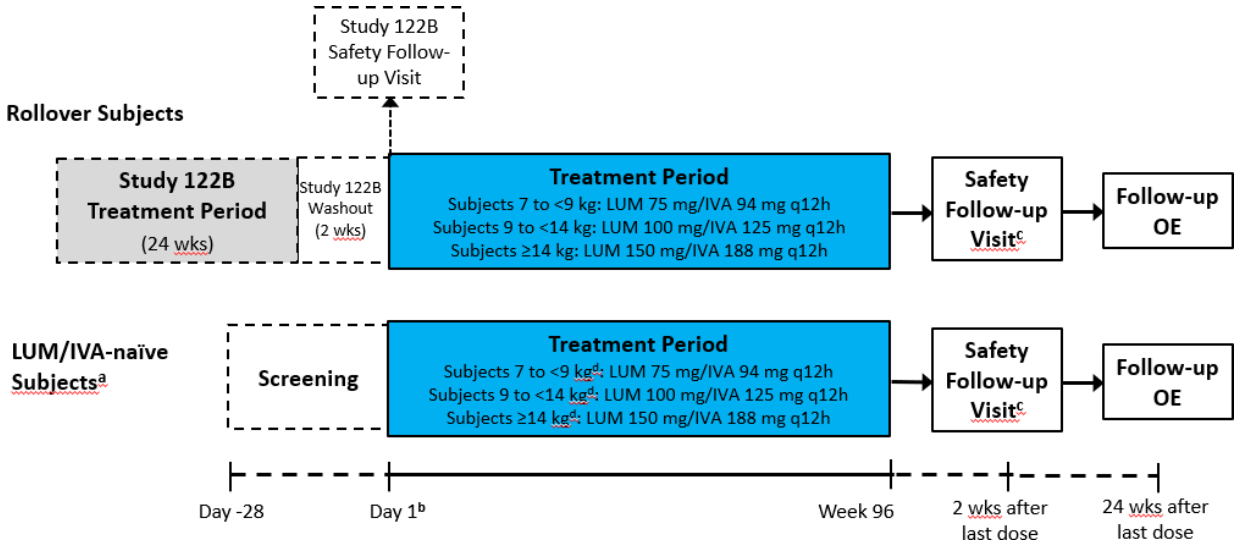
   Note: Ongoing participation in a noninterventional study (including observational studies) is permitted.
8. Use of restricted medication or food within specified duration before the first dose of LUM/IVA as defined in Section 9.4.
9. An adequate slit-lamp examination could not be conducted at the Screening OE.
10. History of cataract/lens opacity or evidence of cataract/lens opacity determined to be clinically significant by a licensed ophthalmologist during the OE at screening. The screening OE does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 12 weeks before screening.
11. 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 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 3, multicenter, open-label study in subjects who are 12 to <24 months of age at initiation of LUM/IVA treatment (Figure 9-1). The study will enroll approximately 50 subjects.

Figure 9-1 Study 124 Design



IVA: ivacaftor; LUM: lumacaftor; OE: ophthalmological examination; q12h: every 12 hours; wks: weeks

[a] LUM/IVA naïve subjects (by age group: 18 to <24 months and 12 to <18 months) will be able to enroll in Study 124 once minimum enrollment has been met for Study 122B (n = 10 subjects in each age group) and after an assessment of safety data from Study 122B through Week 12 for ≥5 subjects in each age group.

[b] For Rollover Subjects, the Day 1 Visit should be the same day as the Safety Follow-up Visit in Study 122B.

[c] The Safety Follow-up Visit will not be required for subjects transitioning to commercial LUM/IVA (Section 9.1.3).

[d] For LUM/IVA-naïve subjects, doses will be determined by weight at screening.

Rollover Subjects

Subjects who participated in Study 122B and meet all eligibility requirements will rollover into Study 124.

Timing of Day 1 Visit

For rollover subjects at sites activated by the Study 122B Safety Follow-up Visit, their Study 124 Day 1 Visit will be on the **same day** as their Study 122B Safety Follow-up Visit. Any Study 124 Day 1 assessments that are specified to be performed at the Study 122B Safety Follow-up Visit do not need to be repeated.

If the Study 124 Day 1 Visit **does not coincide** with the Study 122B Safety Follow-up Visit, and if Study 124 Day 1 is ≤9 days after the Study 122B Safety Follow-up Visit, the Study 124 Day 1 assessments do not need to be repeated. If Study 124 Day 1 is >9 days after the Study 122B Safety Follow-up Visit, the subject will complete all Study 124 Day 1 assessments (except the OE if it was performed ≤12 weeks before the Study 124 Day 1 Visit).

LUM/IVA-naïve Subjects

Subjects who did not participate in Study 122B and are 12 to <24 months of age at Study 124 Day 1 can enroll by age group:

- Subjects who are 18 to <24 months of age can enroll in Study 124 after a minimum of 10 subjects (aged 18 to <24 months) have enrolled in Study 122B, and after an assessment of safety data from Study 122B through Week 12 for ≥5 subjects aged 18 to <24 months.
- Subjects who are 12 to <18 months of age can enroll in Study 124 after a minimum of 10 subjects (aged 12 to <18 months) have enrolled in Study 122B, and after an assessment of safety data from Study 122B through Week 12 for ≥5 subjects aged 12 to <18 months.

Note: Subjects 18 to <24 months of age will start enrolling in Study 124 before any subjects 12 to <18 months of age enroll as a result of the staggered timing as a result of the study design in Study 122, which includes sequential age cohorts.

9.1.1 Screening (LUM/IVA-naïve Subjects Only)

Screening Visit assessments are listed in Table 3-2.

Screening will occur within 28 days before administration of LUM/IVA. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from each subject's parent or legal guardian.

To prepare for study participation, subject's parent or legal guardian will be instructed on the study restrictions (Section 9.4).

9.1.1.1 Repetition of Screening Assessment(s)

Repetition of any screening assessment 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 LFT levels, which may be retested within 14 days of the original Screening Visit date.
- If an adequate slit-lamp examination could not be conducted (Section 11.4.6).
- If QTc exceeds 450 msec at screening (see Section 8.2.2, exclusion criterion 5), 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.

If repeat values of the individual assessment(s) are within the eligibility criteria and completed within the Screening Period window or extended screening window (Section 9.1.1.2), then the subject is eligible for the study.

9.1.1.2 Extension of Screening Period Window

A subject may have the Screening Period window extended by 2 weeks after approval by the medical monitor or authorized designee for the following reasons:

- Repetition of the Screening Period assessments (Section 9.1.1.1)
- Unexpected operational or logistical delays (e.g., delayed drug shipment)
- To account for exclusionary events that may not reflect the subject's true baseline due to an acute event, which may resolve
- Scheduling of the OE (Section 11.4.6)
- Availability or malfunction of required equipment or technician error

The screening window can be extended by 4 weeks if a slit-lamp examination must be repeated (Section 9.1.1.1 and Section 11.4.6).

9.1.1.3 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 *CFTR* genotyping, sweat chloride testing, and the OE (if performed within the last 3 months before the Screening Visit). Subjects may only be rescreened once. If a subject is rescreened, the new screening window date will begin once the first rescreening assessment has been initiated.

9.1.2 Treatment Period

Treatment Period assessments are listed in Table 3-1 for Rollover Subjects and **Error! Reference source not found.** for LUM/IVA-naïve Subjects. Subjects will be outpatients during the Treatment Period. All visits and telephone contacts should occur within the windows specified.

The Treatment Period is 96 weeks; LUM/IVA will be administered every 12 hours (q12h) from Day 1 up to Week 96. LUM/IVA dose and administration details are provided in Section 9.6.

Procedures for subjects who prematurely discontinue LUM/IVA treatment are described in Section 9.1.4.

9.1.3 Follow-up

Safety Follow-up Visit

Subjects will have a Safety Follow-up Visit 2 weeks (± 4 days) after the last dose of study drug. Safety Follow-up Visit assessments are listed in Table 3-1 for the Rollover Subjects and **Error! Reference source not found.** for the LUM/IVA-naïve Subjects.

The Safety Follow-up Visit is required for:

- Subjects who complete their Early Termination of Treatment (ETT) Visit <10 days after the last dose of LUM/IVA (Section 9.1.4)
- Subjects who interrupt LUM/IVA treatment and complete their Week 96 Visit <10 days after the last dose of LUM/IVA

The Safety Follow-up Visit is not required for subjects who continue onto commercially available, physician-prescribed LUM/IVA within 2 weeks (± 4 days) of completing LUM/IVA treatment at the Week 96 or ETT Visit.

Follow-up Ophthalmological Examination

Subjects will have a Follow-up OE 24 weeks (± 14 days) after the last dose of study drug.

9.1.4 Early Termination of Treatment OR Early Discontinuation

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 96 Visit and the Safety Follow-up Visit, if applicable. The assessments to be completed are shown in Table 3-1 and Table 3-2. If the ETT Visit occurs ≥10 days after the last dose of LUM/IVA, then a Safety Follow-up Visit will not be required. Additional safety assessments may also be performed at the discretion of the investigator, including possible consultation with a specialist consultant. The Vertex medical monitor will be informed about these additional assessments, and any additional data collected (e.g., as the result of an outside consultation) will be considered part of the study record to provide the most complete safety profile of the study drug.

Subjects who become eligible to receive commercially available LUM/IVA by prescription from a physician and who choose to continue onto commercially available LUM/IVA before completion of the study 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. Subjects who continue onto commercially available LUM/IVA will complete the Follow-up OE 24 weeks (± 14 days) after the last dose of study drug.

9.1.5 Independent Data Monitoring Committee

Safety and tolerability data will be reviewed by an independent data monitoring committee (IDMC) to ensure the safety of the subjects (Section 12.3.6.2). Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be in the IDMC charter. The IDMC charter will be finalized before the first subject is enrolled.

9.1.6 Use of Remote Measures in Extenuating Circumstances

Study visits should be performed in the clinic as specified in Table 3-1 or Table 3-2, if at all possible. However, under extenuating circumstances, remote measures may be implemented (e.g., if a subject is unable to travel to the study site due to safety concerns and/or local restrictions related to COVID-19 or other emerging events). The decision whether to conduct study visits remotely or in clinic will be at the discretion of the investigator.

Whenever local regulations or site practice do not allow remote measures, visits will be conducted at the site.

Remote measures that may be implemented include, but are not limited to:

- Consent or reconsent may be obtained remotely in writing (or verbally, with follow-up written confirmation), as allowed by local regulations.
- Study drug may be shipped directly from the site to the subject, as applicable and as allowed by local regulations.

- Study visits may be conducted as in-home visits by qualified personnel.
- Study assessments may be performed or overseen by qualified personnel conducting the in-home visits.
- Remote monitoring visits may be implemented as applicable (including remote source data verification) and as allowed per local regulations
- Blood samples for safety assessments may be collected and analyzed by local laboratories.
- Weight and stature may be assessed by the subject's caregivers using medical grade scales and stadiometers.

9.2 Method of Assigning Subjects to Treatment Groups

This is an open-label study.

9.3 Rationale for Study Elements

9.3.1 Study Design

Vertex has established efficacy, safety, and PK profiles for LUM/IVA in subjects 2 years of age and older with CF, homozygous for *F508del* (Studies 103, 104, 109, and 115). Because the underlying genetic and molecular etiology of the disease is identical between younger and older patients, and the impact of CFTR protein dysfunction is likely to be comparable, extrapolation of efficacy from older to younger patients is appropriate, and PK studies in younger patients, together with safety studies, can provide adequate information for use.[14]

Safety and PK profiles for LUM/IVA have been established in subjects aged 2 years and older with CF, homozygous for *F508del* (Study 115). Study 122, a Phase 3, 2-part open-label study, which includes a 24-week Treatment Period in Part B, is designed to obtain PK and safety information to support a proposed indication expansion of LUM/IVA in subjects who are 12 to <24 months of age with CF, homozygous for *F508del.*

Long-term safety and efficacy was established in subjects aged 6 years and older with CF, homozygous for *F508del,* in Study 110, the open-label rollover study for parent Studies 109 and 011B. Evaluation of long-term safety in subjects aged 2 years and older with CF, homozygous for *F508del*, is currently ongoing in Study 116, the open-label rollover study for parent Study 115.

Study 124 is a Phase 3, open-label, multicenter study in subjects with CF, homozygous for *F508del*, who are 12 to <24 months of age when LUM/IVA treatment is initiated. This study, which includes a 96-week Treatment Period, is designed to evaluate the long-term safety of LUM/IVA when treatment is initiated between 12 and 24 months of age.

9.3.2 Study Drug Dose and Duration

Dose of LUM/IVA

Study 122 Part A (Study 122A) was designed to characterize the safety and PK of LUM and IVA in subjects 12 through <24 months of age. The plasma concentration versus time data from Study 122A is intended to inform the appropriateness or necessary adjustment of planned doses for Studies 122B and 124. As data from Study 122B become available, the doses may be modified for subjects in Study 124. A population PK model with allometric scaling of clearance and volume of distribution as a function of weight was used to project exposures of LUM and

IVA for comparison with clinical experiences with both drugs and to select doses to be evaluated in this study population. No safety issues were identified in prior clinical or nonclinical studies that would preclude the dosing regimen proposed for Study 124.

Duration of Dosing

Subjects who receive LUM/IVA in Study 124 may receive treatment for up to 120 weeks (for Rollover Subjects: 24 weeks in Study 122B and 96 weeks in Study 124; for LUM/IVA-naïve Subjects: 96 weeks in Study 124), thus providing information on the long-term safety of LUM/IVA in subjects aged 1 year and older with CF, homozygous for *F508del*.

9.3.3 Study Assessments

The safety assessments are standard parameters for clinical studies in drug development and are generally recognized as reliable, accurate, and relevant to the study of subjects with CF. OEs were added as part of safety monitoring. Assessments were added to evaluate the PD effects of LUM/IVA. The following PD and efficacy-related assessments are standard assessments used in studies in the LUM/IVA development program: sweat chloride and growth parameters, including weight, length, and BMI. Rationale is provided below for OEs and additional assessments (exocrine pancreatic function and markers of intestinal inflammation).

Ophthalmological Examinations: A juvenile rat toxicity study performed to support dosing of IVA in subjects <2 years of age demonstrated lens opacities in some animals.[15] Prior studies in rats and dogs of older age did not demonstrate similar findings. Given substantial differences between human and rat lens development, the finding is of unlikely relevance to humans. Periodic OEs for pediatric subjects receiving IVA or IVA in combination with a CFTR corrector are being performed to confirm this interpretation. The overall data acquired to date does not suggest an association between IVA treatment and cataract development.

Exocrine Pancreatic Function: The pancreas is 1 of the earliest and most seriously affected organs in patients with CF who are homozygous for *F508del,* the vast majority of whom develop pancreatic insufficiency.

- FE-1: FE-1 is a diagnostic measure of pancreatic exocrine sufficiency, with levels <200 µg/g considered consistent with pancreatic insufficiency. The increasing use of FE-1 in the clinic is a result of the ease of collecting samples (relative to other methods, e.g. 24-hour fecal fat) for its assessment and the establishment of diagnostic cutoffs for pancreatic exocrine function.[16] FE-1 represents a feasible measure to evaluate exocrine pancreatic function during the study, with the hypothesis that treatment with LUM/IVA may rescue a degree of pancreatic function, resulting in increased FE-1 levels over the course of the study.
- IRT: Trypsin and trypsinogen are proteins produced by the pancreas that can be detected in the blood via the IRT assay. Evaluation of IRT is used in clinical practice as the basis of newborn screening for CF, wherein elevated levels at birth are associated with disease. Over time, however, patients with CF show a longitudinal decline in IRT with nondetectable levels observed around 5 years of age, indicating a loss of pancreatic function.[17] Blood samples for IRT testing will be collected at multiple time points to evaluate potential changes in exocrine pancreatic function.

Markers of Intestinal Inflammation: Fecal samples will be collected to investigate biomarkers related to intestinal inflammation in CF patients, including but not limited to fecal calprotectin. Fecal calprotectin has been shown to be increased in pediatric patients with CF.[18] These data

support the concept that intestinal inflammation is a feature of CF and that intestinal inflammation can be monitored by measuring non-invasive biomarkers such as fecal calprotectin in clinical studies with CF patients.

9.4 Study Restrictions

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

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

Table 9-1 Study Restrictions

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

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.

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

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

Each investigator should evaluate the benefit-risk ratio of using CYP3A, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 substrates with LUM and IVA and discuss their use with the medical monitor or authorized designee.

9.5 Prior and Concomitant Medications

Information regarding all prior and concomitant medications, including the subject's CF medications, other medications, and herbal and naturopathic remedies administered from 28 days before the first dose through the Safety Follow-up Visit, if applicable, 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 the Safety Follow-up Visit, 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. Note: PERT doses may be adjusted during this study.
- While the etiology of respiratory events associated with LUM/IVA is not yet known, data from healthy subjects in Study 009 Cohort 4 suggest that treatment with short-acting

bronchodilators may reverse the initial transient decline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) when dosed with LUM/IVA. Subjects may be prescribed a short-acting bronchodilator in accordance with local drug labeling (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.

9.6 Administration

LUM/IVA will be administered orally according to the planned doses and weight bounds shown in Table 9-2. Changes to study drug dose(s) and/or weight bounds based on results from Study 122 may be communicated to site personnel through a memorandum entitled "Justification for Dose Selection."

Table 9-2 Study Drug Administration: Planned Doses

Dose	Subject's Weight[a]	Time	LUM/IVA (Number of Stick Packs)
LUM 75 mg/IVA 94 mg q12h	7 to <9kg	AM	1 stick pack
		PM	1 stick pack
LUM 100 mg/IVA 125 mg q12h	9 to <14 kg	AM	1 stick pack
		PM	1 stick pack
LUM 150 mg/IVA 188 mg q12h	≥14 kg	AM	1 stick pack
		PM	1 stick pack

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

[a] Doses may be adjusted upward based on weight gain; however, no downward dose adjustments will be made if a subject's weight decreases. For example, if a subject weighs <14 kg at screening and subsequently weighs ≥14 kg at 2 consecutive study visits, the dose will be adjusted to LUM 150 mg/IVA 188 mg q12h at the second study visit when weight ≥14 kg.

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 q12h (± 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 Reference Manual. Each dose will be composed 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. At the Day 1 Visit, all LUM/IVA-naïve subjects will be observed for 4 hours after the LUM/IVA dose.

4. On days of scheduled visits, with the exception of afternoon visits addressed below, the morning LUM/IVA dose will be administered at the site after any predose assessments have been completed.
5. If a subject's scheduled visit is to occur in the afternoon, the following guidelines must be used for administering either the morning or evening dose:
    - If the dose in the clinic will be within 6 hours of the subject's scheduled morning LUM/IVA dose, the subject should withhold their morning dose and the morning dose will be administered in the clinic.
    - If the dose in the clinic will be more than 6 hours after the subject's scheduled morning LUM/IVA dose, the subject should take the morning dose at home and the evening dose will be administered in the clinic. In this event, all assessments will be collected relative to the evening dose.
6. For visits after the Day 1 Visit, subjects will be instructed to bring all used and unused LUM/IVA materials to the site; LUM/IVA will be dispensed at each visit, as appropriate.

At the Week 96 Visit, the LUM/IVA dose will NOT be administered. The last LUM/IVA dose will be the previous dose (e.g., evening dose) administered before the Week 96 Visit.

9.7 Dose Modification for Toxicity

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

9.8 Study Drug Interruptions

If study drug dosing must be interrupted for more than 72 hours, the Vertex medical monitor must be notified. In these instances, study drug dosing may resume only after approval by the Vertex medical monitor. Specific instructions on interruption for elevated LFT levels are provided in Section 11.4.3.

9.9 Removal of Subjects

Subjects may withdraw from the study at any time at the request of the parent or legal guardian. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. If a subject has been withdrawn from study drug treatment, the subject will continue to be followed as described in Section 9.1.4, provided that the subject's parent or legal guardian 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 a Safety Follow-up Visit, if applicable (see Section 9.1.3), and follow up with the subject's parent or legal guardian regarding any unresolved AEs.

If the subject's parent or legal guardian withdraws consent for the study, no further evaluations should be performed, and no additional data should be collected. Vertex may retain and continue using the study data and samples after the study is over and may use the samples and information in the development of the study compound, and for other drugs and diagnostics, in publications

and presentations, and for education purposes. If the subject's parent or legal guardian withdraws the subject from the study, the study data and samples collected will remain part of the study. A subject's parent or legal guardian will not be able to request the withdrawal of the subject's information from the study data. A subject's parent or legal guardian may request destruction of the samples collected from the subject during the study as long as those samples can be identified as the subject's samples.

9.10 Replacement of Subjects

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

10 STUDY DRUG INFORMATION AND MANAGEMENT

10.1 Preparation and Dispensing

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

10.2 Packaging and Labeling

Vertex will supply the LUM/IVA granules in stick packs. Study drug labeling will be in compliance with applicable local and national regulations. Additional details about packaging, labeling, and dispensing for LUM/IVA will be in the Pharmacy Manual.

10.3 Study Drug Supply, Storage, and Handling

Table 10-1 provides the study drug information. The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for as described in Section 10.4. Detailed instructions regarding the storage, handling, and dispensation of LUM/IVA will be provided in the Pharmacy Manual.

Table 10-1 Study Drug

Drug Name	Formulation/ Route	Packaging (Formulation Strength)	How Supplied
LUM/IVA	Granules/ oral	75-mg LUM/94-mg IVA granules	Supplied in 1 stick pack
LUM/IVA	Granules/ oral	100-mg LUM/125-mg IVA granules	Supplied in 1 stick pack
LUM/IVA	Granules/ oral	150-mg LUM/188-mg IVA granules	Supplied in 1 stick pack

IVA: ivacaftor; LUM: lumacaftor

10.4 Drug Accountability

The pharmacist or designated study site staff will maintain information about the dates and amounts of (1) study drug received; (2) study drug dispensed to the subjects; and (3) study drug returned by the subject's parent or legal guardian. The subject's parent or legal guardian 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. The study monitor will review study drug records and inventory throughout the study. If a site uses a site-specific drug accountability system and/or process, including processes associated with the destruction of returned materials, the process must be documented and approved by Vertex. The study monitor must review the drug accountability documentation on a regular basis. The study monitor will promptly communicate to Vertex any discrepancies he/she is unable to resolve with the site.

10.5 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subject's parent or legal guardian until the study monitor has performed drug accountability. The investigator will ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Vertex. Destruction will be adequately documented.

10.6 Compliance

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

If there is 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.

10.7 Blinding and Unblinding

This is an open-label study.

However, the site and the subject's parent or legal guardian should not be informed of a subject's study-related sweat chloride (except if needed to confirm eligibility), IRT, FE-1, and markers of intestinal inflammation results during the study even if the subject permanently discontinued treatment.

11 ASSESSMENTS

The schedule of assessments is shown in Table 3-1 for Rollover Subjects and Table 3-2 for LUM/IVA-naïve Subjects.

11.1 Subject and Disease Characteristics

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

For Rollover Subjects, medical history will be taken from Study 122B. For LUM/IVA-naive Subjects, medical history will be elicited from each subject's parent or legal guardian 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.

In addition, the following historical data will be collected from birth to screening (for all subjects):

- Maternal/pregnancy history: complications in pregnancy, gestational age at delivery, method of delivery, and presence of meconium ileus (if documented in subject's clinical chart)
- Routine/quarterly CF clinic visit measurements for length/height and weight. Note: Measurements taken during sick visits or hospitalizations will not be collected.
- The dates and indications for all CF-related hospitalizations
- Any use (yes or no) of the following medications:
    - Inhaled antibiotics (e.g., tobramycin, aztreonam, or colimycin)
    - Nebulized hypertonic saline (any %)
    - Nebulized dornase alfa
    - Oral azithromycin (anti-inflammatory dosing M/W/F)
- Historical pancreatic status measurements (e.g., prior FE-1 levels)

In addition, the subject's parent or legal guardian will be asked during screening to provide the height of the subject's biological parents.

11.2 Pharmacodynamics

11.2.1 Sweat Chloride

Collection of sweat samples will be performed using an approved collection device. Sweat samples will be sent to a central laboratory for testing and interpretation of results. Specific instructions for collection, handling, processing, and shipping of sweat chloride samples to the central laboratory will be provided separately. At each time point, 2 samples will be collected, 1 sample from each arm (left and right).

11.3 Exploratory Assessments

11.3.1 Growth Parameters

Weight and length/height will be assessed and BMI will be derived. Length/height and weight must be measured with the subject in a dry diaper or dry underclothes only. If the subject is >2 years of age and can stand unassisted and follow directions, standing height should be measured; otherwise recumbent length should be measured. Length should be measured while the subject is supine by measuring from the crown of the head to the bottom of the feet, with the hips and legs straightened. BMI will be calculated using the following equation: BMI (kg/m^2) = body weight (kg) ÷ $stature^2$ (m^2). Z-scores adjusting for age and sex in weight, length/height, and BMI, as well as weight-for-length z-score will be derived. Formulas for calculating z-scores will be provided in the statistical analysis plan (SAP).

11.3.2 Measures of Pancreatic Function

11.3.2.1 Fecal Elastase-1

Fecal samples for assessment of FE-1 may be collected at the study site during the study visit or by the subject's caregiver up to 48 hours before the study visit (e.g., at home) and brought to the study visit. For the LUM/IVA-naïve subjects, the sample collected before the first dose of study

drug can either be collected at screening or up to 48 hours before the Day 1 study visit (as described in Table 3-2). Specific instructions for the collection, processing, and shipment of samples will be provided in a separate Laboratory Manual.

11.3.2.2 Immunoreactive Trypsin and Trypsinogen

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

11.3.3 Markers of Intestinal Inflammation

Fecal samples for assessment of fecal calprotectin (and other markers of intestinal inflammation, if applicable) may be collected at the study site during the study visit or by the subject's caregiver up to 48 hours before the study visit (e.g., at home) and brought to the study visit. For the LUM/IVA-naïve subjects, the sample collected before the first dose of study drug can either be collected at screening or up to 48 hours before the Day 1 study visit (as described in Table 3-2). Specific instructions for the collection, processing, and shipment of samples will be provided in a separate Laboratory Manual.

11.4 Safety

Safety evaluations will include AEs, clinical laboratory assessments (serum chemistry and hematology), clinical evaluation of vital signs, pulse oximetry, standard 12-lead ECGs, physical examinations, and OEs.

11.4.1 Adverse Events

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

11.4.2 Clinical Laboratory Assessments

Blood samples will be analyzed at a central laboratory. Although blood samples are to be 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 11.4.3).

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

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

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology
Glucose	Hemoglobin
Blood urea nitrogen	Platelets
Creatinine	Total white blood cell count
Sodium	Differential (absolute and percent):
Potassium	Eosinophils
Calcium	Basophils
Total bilirubin, direct bilirubin	Neutrophils
Alkaline phosphatase	Lymphocytes
Aspartate aminotransferase (AST)	Monocytes
Alanine aminotransferase (ALT)	
Lactate dehydrogenase	
Gamma glutamyl transferase (GGT)	
Total protein	
Albumin	
Creatine kinase	
Amylase	
Lipase	

Clinical laboratory assessments from screening (for LUM/IVA-naïve subjects) 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 for LUM/IVA-naïve subjects only): If a historic genotype result is not available at screening or if the historic genotype result is not approved by the Vertex medical monitor, CF genotyping will be performed on a subject to confirm the subject is homozygous for *F508del*. Note: Newborn screening genotype results are not sufficient for eligibility.

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

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.

11.4.3 Elevation of Liver Function Test Parameters

Mandatory Liver Function Testing

Liver function testing (ALT, AST, gamma-glutamyl transferase [GGT], alkaline phosphatase [ALP], and total bilirubin) must be performed while subjects are receiving LUM/IVA treatment (see Table 3-2 and Section 11.4.2). These blood samples should be processed and shipped immediately as per the Laboratory Manual.

Rollover subjects who had a study drug interruption at the Week 24 Visit of Study 122B or subjects who resumed study drug in Study 122B after a study drug interruption due to elevated transaminases but who did not complete the required 4 weeks of rechallenge with LUM/IVA (due to <4 weeks remaining in the Study 122B Treatment Period) will be reviewed by the Vertex medical monitor and should continue to be monitored based on the guidance for study drug interruption and resumption provided below. For example, 4 weeks of rechallenge with LUM/IVA should be completed, and any other assessments deemed necessary by the investigator in conjunction with the Vertex medical monitor may be performed. If a subject has a study drug interruption that spans the time period between Week 24 of Study 122B and Day 1 of Study 124, approval from the Vertex medical monitor or designee is required before resumption of LUM/IVA in Study 124.

Subjects with new ALT or AST elevations of ≥3 × ULN and clinical symptoms will be followed closely, including repeat confirmatory testing performed by the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT and AST levels, as clinically indicated. If a subject cannot return to the site for liver function testing, a local laboratory may be used. Elevations in LFTs (ALT or AST ≥3 × ULN) at the local laboratory must be reported immediately to the Vertex medical monitor or designee, AND the subject must have the tests repeated and sent to the central laboratory as soon as possible (ideally within 48 to 72 hours).

Study Drug Interruption

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

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

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

Resumption of Study Drug

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

Discontinuation of Study Drug

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

11.4.4 Physical Examinations and Vital Signs

A PE of all body systems and vital signs assessment will be performed at screening and select study visits. At other visits, symptom-directed PEs and symptom-directed vital signs assessments can be performed at the discretion of the investigator or healthcare provider.

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

An abbreviated PE will be performed at select study visits. The abbreviated PE will include an assessment of the following body systems: head/neck/thyroid, EENT, cardiovascular system, respiratory system, skin, and abdomen.

Vital signs include blood pressure (systolic and diastolic), temperature (any clinically acceptable method may be used, however, the same method should be used at each visit), pulse rate, respiration rate, and pulse oximetry. The subject should rest for at least 5 minutes, if possible, before vital signs are measured.

Weight and length/height will be assessed and BMI will be derived. Length/height and weight must be measured with the subject in a dry diaper or dry underclothes only. Recumbent length should be measured for subjects ≤2 years, or until the subject is comfortable with having standing height measured. Recumbent length should be measured while the subject is supine by measuring from the crown of the head to the bottom of the feet, with the hips and legs straightened. Standing height should be measured for subjects >2 years of age or once the subject is comfortable with the procedure.

11.4.5 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout. 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 ECG will be done before any other procedures that may affect heart rate, such as blood draws.
- The subject will be instructed to rest for at least 5 minutes before having an ECG.
- The test should be performed in the supine position

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

To ensure safety of the subjects, the investigator will make comparisons of the ECG findings to baseline measurements. Repeat ECGs will be performed as deemed appropriate. Subject eligibility to continue in the study will be evaluated.

11.4.6 Ophthalmological Examination

OEs must be conducted by a licensed ophthalmologist, preferably a pediatric ophthalmologist. The OE includes an examination of the lens with a slit lamp.

For the LUM/IVA-naïve subjects, the screening OE 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 OE, the subject must not be enrolled. The screening OE does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 12 weeks before the Screening Visit.

A Follow-up OE will be performed approximately 24 weeks after the last dose of LUM/IVA.

11.4.7 Contraception and Pregnancy

Not applicable

12 STATISTICAL AND ANALYTICAL PLANS

12.1 Sample Size and Power

No formal sample size calculations have been performed for this study. The study will enroll approximately 50 subjects to provide data for the assessment of long-term safety in the target patient population, as requested by a regulatory agency.

12.2 Analysis Sets

124 All Subjects Set: All subjects who are enrolled or dosed in Study 124

124 Safety Set: All subjects who are exposed to any amount of study drug in Study 124

124 Full Analysis Set (124 FAS): All subjects who are enrolled and dosed in Study 124

12.3 Statistical Analysis

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

Statistical analysis and presentation details will be provided in the SAP that will be finalized before the data cut/lock. Additional analysis deemed necessary but not specified in the protocol will be defined in the SAP.

12.3.1 General Considerations

All individual subject data will be presented in data listings based on the 124 All Subjects Set.

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

Categorical variables will be summarized using counts and percentages.

Baseline value will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected on or before the first dose of LUM/IVA in Study 124.

For sweat chloride, values at each visit will be based on averaged measurements from left and right arms as specified in Section 11.2.1. For Rollover Subjects, baseline will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected on or before the first dose of LUM/IVA in Study 124. For LUM/IVA-naïve Subjects, baseline will be defined as the average of the values at screening and the pretreatment measurement on Day 1 of Study 124. 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.

Current Study Period starts from the first dose of study drug in Study 124 to the last day in Study 124.

The **Treatment-emergent (TE) Period for the Current Study Period** starts on or after the first dose date of study drug in Study 124 to 14 days (inclusive) after the last dose of study drug in Study 124 or up to the last day in Study 124, whichever occurs first.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

Number of subjects in the following categories for the population will be provided:

- 124 All Subjects Set
- 124 Safety Set
- 124 FAS

Number and percentage (based on the 124 Safety Set) of subjects in each of the following categories will also be provided:

- Enrolled but never dosed (number of subjects only)
- Completed treatment
- Prematurely discontinued treatment and the reason for discontinuation
- Last scheduled on-treatment visit completed for subjects who discontinued treatment
- Completed study (i.e., completed the Safety Follow-up Visit)
- Prematurely discontinued the study and reason for discontinuation

12.3.2.2 Demographics and Baseline Characteristics

Demographics, baseline characteristics, and medical history will be summarized for the 124 Safety Set.

Medical history will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT).

12.3.2.3 Prior and Concomitant Medications

Medications used will be coded using the World Health Organization-Drug Dictionary (WHO-DD) and categorized as the following:

Prior medication: Any medication that started before the date of the first dose of study drug in Study 124

Concomitant medication: Medication continued or newly received during the TE Period of the Current Study Period

Post-treatment medication: Any medication continued or newly received after the end of the TE Period of the Current Study Period

A given medication may be classified as prior; concomitant; post-treatment; both prior and concomitant; both concomitant and post-treatment; and prior, concomitant, and post-treatment. Incidence of prior medication will be summarized based on the 124 Safety Set by (1) Preferred Name; (2) anatomical therapeutic chemical (ATC) level 1; ATC level 2; and Preferred Name. Incidence of concomitant medication will be summarized based on the 124 Safety Set for the Current Study Period by (1) Preferred Name; (2) ATC level 1; ATC level 2; and Preferred Name.

Details for imputing missing or partial start and/or stop dates of medication will be in the SAP.

12.3.2.4 Study Drug Exposure and Compliance

Study Drug Exposure

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

Duration of study drug exposure as well as number of sticks administered, defined as (total number of sticks dispensed) − (total number of sticks returned), will be summarized descriptively overall based on the 124 Safety Set for the Current Study Period. Additionally, the total duration of treatment exposure, defined as the sum of the subject's duration of treatment exposure and expressed in patient-years (1 patient-year is defined as 1 patient with 48 weeks of treatment), will be provided. Duration of exposure will also be summarized as a categorical variable.

Study Drug Compliance

Study drug compliance will be calculated as follows: 100 × (1 − [total number of days of study drug interruption in the Current Study Period] / [duration of study drug exposure in the Current Study Period]). The total number of days of study drug interruption is defined as the sum of (number of days of each study drug interruption in the Current Study Period), where number of days of each study drug interruption is defined as the interruption end date − the corresponding interruption start date + 1.

Treatment compliance percentages will be summarized descriptively (number, mean, SD, median, min, and max) overall based on the 124 Safety Set for the Current Study Period. The number and percentage of subjects whose compliance is <80% or ≥80% will be summarized.

12.3.3 Secondary Endpoint Analysis

12.3.3.1 Absolute Change From Baseline in Sweat Chloride

Raw values and absolute change from baseline in sweat chloride at each visit of the Current Study Period will be summarized descriptively based on the 124 FAS overall. Descriptive statistics, including number of subjects, mean, SD, median, min, and max, along with the 95% CI based on Normal approximation, will be provided for the absolute change from baseline values. The mean (95% CI) of the absolute change from baseline values will be plotted.

12.3.4 Exploratory Endpoint Analysis

12.3.4.1 Absolute Change From Baseline in Growth Parameters

Raw values and absolute change from baseline in the following endpoints at each visit of the Current Study Period will be summarized descriptively based on the 124 FAS overall. In addition, 95% CI of the absolute change from baseline values will be provided.

- BMI-for-age z-score and BMI

- Weight-for-age z-score and weight
- Length/height-for-age z-score and length/height
- Weight-for-length z-score

12.3.4.2 Absolute Change From Baseline in Markers of Pancreatic Function

Raw values and absolute change from baseline in the following endpoints at each visit of the Current Study Period will be summarized descriptively based on the 124 FAS overall:

- FE-1 levels
- Serum IRT levels

In addition, number and percentage of subjects with FE-1 levels consistent with pancreatic insufficiency, defined as FE-1 value <200 µg/g, will be provided at baseline and at each visit of the Current Study Period. The number and percentage of subjects with shift changes from baseline at each visit of the Current Study Period will be summarized as well.

12.3.4.3 Absolute Change From Baseline in Fecal Calprotectin

Raw values and absolute change from baseline in fecal calprotectin levels at each visit of the Current Study Period will be summarized descriptively based on 124 FAS overall.

12.3.5 Safety Analysis

The overall safety profile of LUM/IVA will be assessed in terms of the following safety and tolerability endpoints:

- AEs
- Clinical laboratory measurements (serum chemistry and hematology)
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry
- OEs

Safety endpoints will be summarized descriptively based on the 124 Safety Set.

All listings will be provided based on the 124 All Subjects Set.

12.3.5.1 Adverse Events

AEs will be classified as pretreatment AEs or treatment-emergent adverse events (TEAEs), defined as follows:

Pretreatment AE: Any AE that started before the first dose date of study drug in Study 124

TEAE: Any AE that worsened (either in severity or seriousness) or that was newly developed on or after the first dose date of study drug through the end of the TE Period of the Current Study Period

Post-treatment AE: Any AE that increased in severity or that newly developed after the TE Period of the Current Study Period

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

Details for imputing missing or partial start dates of AEs will be described in the SAP.

TEAE summaries will be presented using number and percentages of subjects for the Current Study Period based on the 124 Safety Set overall.

An overview of the TEAE profile will be provided, including total number of TEAEs, with number and percentage of subjects for the following categories: (1) all TEAEs; (2) Grade 3/4 TEAEs; (3) TEAEs by relationship; (4) TEAEs by maximum severity; (5) TEAEs leading to treatment interruption; (6) TEAEs leading to treatment discontinuation; (7) serious TEAEs; (8) related serious TEAEs; and (9) TEAEs leading to death.

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

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

Summaries will be presented by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with any event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once, only the maximum severity level will be presented in the severity summaries, and the worst/highest relationship level in the relationship summaries.

In addition, listings containing individual subject data for all TEAEs leading to treatment interruption, TEAEs leading to treatment discontinuation, deaths, and serious adverse events (SAEs) will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

12.3.5.2 Clinical Laboratory Assessments

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

The number and percentage of subjects meeting the threshold analysis criterion during the TE Period of the Current Study Period will be summarized based on the 124 Safety Set overall. The threshold analysis criteria will be provided in the SAP.

In addition, a listing containing individual subject hematology and chemistry values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled visits.

12.3.5.3 Electrocardiogram

For the ECG measurements, the raw values and change from baseline values will be summarized at each visit of the Current Study Period overall, for the following standard digital ECG measurements: PR, QT, and QT corrected for HR (QTc) intervals (Fridericia's correction), QRS duration, and HR. In addition, the mean value (95% CI) at each visit will be plotted for QTcF.

The number and percentage of subjects meeting the threshold analysis criterion during the TE Period of the Current Study Period will be summarized based on the 124 Safety Set overall. The threshold analysis criteria will be provided in the SAP.

12.3.5.4 Vital Signs

For the vital signs measurements, the raw values and change from baseline values will be summarized at each visit of the Current Study Period overall, for the following parameters: systolic and diastolic blood pressure (mm Hg), temperature (°C), pulse rate (beats per minute), respiratory rate (breaths per minute), weight, length/height, and BMI.

The number and percentage of subjects meeting the threshold analysis criterion during the TE Period of the Current Study Period will be summarized based on the 124 Safety Set overall. The threshold analysis criteria will be provided in the SAP.

12.3.5.5 Physical Examination

PE findings will be presented in individual subject data listings only.

12.3.5.6 Pulse Oximetry

For the pulse oximetry measurements, a summary of raw values and change from baseline values will be provided at each visit of the Current Study Period overall, 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 TE Period of the Current Study Period will be summarized based on the 124 Safety Set overall.

12.3.5.7 Ophthalmological Examinations

OE findings will be presented as a data listing.

12.3.6 Interim and Independent Data Monitoring Committee Analyses

12.3.6.1 Interim Analysis

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.

12.3.6.2 IDMC Analysis

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

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

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

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

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

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

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

13.1.1.3 Documentation of Adverse Events

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

- 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, with the exception of ocular AEs noted during the Follow-up OE.

- For enrolled subjects who do not have a Safety Follow-up Visit, the earliest of
    - 14 days after the last dose of study drug, or
    - the ETT Visit, if that visit is >10 days following the last dose of study drug (see Section 9.1.4)

All subject's parents or legal guardians 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 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

For the purposes of study analysis, if the event has not resolved at the end of the study reporting period (the Safety Follow-up Visit), it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the AE to symptom resolution or until the condition stabilizes.

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: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007, Center for Biologics Evaluation and Research, https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM091977.pdf (Accessed July 2018). When 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 in the vaccine scale. The severity of an AE described by a term that does not appear in this scale will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

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

13.1.1.5 Adverse Event Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug(s). Causality will be classified using the categories 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 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 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 in Table 13-4.

Table 13-4 Classifications for Outcome of an AE

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

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, 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 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 Reporting and Documentation of Serious Adverse Events

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

For SAEs that occur after obtaining informed consent and assent (where applicable) through the Safety Follow-up Visit, 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: globalpatientsafety@vrtx.com (preferred choice)

Fax: +1-617-341-6159

For technical issues related to submitting the form, contact telephone: +1-617-341-6677

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

13.1.2.3 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, IECs, and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to central IECs.

It is the responsibility of the investigator or designee to promptly notify the local IRB/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 be conducted only 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's parent or legal guardian 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 will be limited to the site and the study physician and will 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 US, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated regulations, an executed HIPAA authorization will be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization will 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.

13.2.8 End of Study

The end of study is defined as the last scheduled visit (or scheduled contact) of the last subject.

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 subject. 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.

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.

13.4 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 them, 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 compact disc (CD) or other electronic media will be placed in the investigator's study file.

13.5 Confidentiality and Disclosure

Any and all scientific, commercial, and technical information disclosed by Vertex in this protocol or elsewhere will be considered the confidential and proprietary property of Vertex. The

investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The investigator shall not use such information for any purpose other than determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The investigator understands that the information developed from this clinical study will be used by Vertex in connection with the development of the study drug and other drugs and diagnostics, and therefore may be disclosed as required to other clinical investigators, business partners and associates, the FDA, and other government agencies. The investigator also understands that, to allow for the use of the information derived from the clinical study, the investigator has the obligation to provide Vertex with complete test results and all data developed in the study.

13.6 Publications and Clinical Study Report

13.6.1 Publication of Study Results

Vertex is committed to reporting the design and results of all clinical studies in a complete, accurate, balanced, transparent, and timely manner, consistent with Good Publication Practices (GPP3).[19]

Publication Planning: Vertex staff along with the lead principal investigators (PIs), the steering committee (SC), and/or the publication committee (PC) will work together to develop a publication plan.

Authorship: Authorship of publications will be determined based on the Recommendations for Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states that authorship should be based on the following 4 criteria:[20]

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2. Drafting of the article or revising it critically for important intellectual content;
3. Final approval of the version to be published; and
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet conditions 1, 2, 3, and 4. All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Contributions such as medical writing, enrollment of subjects, acquisition of funding, collection of data, or general supervision of the research group, alone, do not justify authorship.

Contributors: Contributors who meet fewer than all 4 of International Committee of Medical Journal Editors (ICMJE) criteria for authorship will not be listed as authors, but their contribution will be acknowledged and specified either as a group (e.g., “study investigators”) or individually (e.g., “served as scientific advisor”).

Publication Review: As required by a separate clinical study agreement, Vertex must have the opportunity to review all publications, including any manuscripts, abstracts, oral/slide

presentations, and book chapters regarding this study before submission to congresses or journals for consideration.

13.6.2 Clinical Study Report

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

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX19-809-124	Version #: 2.0	Version Date: 12 February 2021
Study Title: A Phase 3, Open-label, and Rollover Study to Evaluate the Long-term Safety and Tolerability of Lumacaftor/Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Homozygous for *F508del* and 12 to <24 Months of Age at Treatment Initiation		

This clinical study protocol has been reviewed and approved by the sponsor.

Printed Name	Title
Signature	Date

15.2 Investigator Signature Page

Protocol #: VX19-809-124	Version #: 2.0	Version Date: 12 February 2021
Study Title: A Phase 3, Open-label, and Rollover Study to Evaluate the Long-term Safety and Tolerability of Lumacaftor/Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Homozygous for *F508del* and 12 to <24 Months of Age at Treatment Initiation		

I have read Protocol VX19-809-124, Version 2.0, and agree to conduct the study according to its terms. I understand that all information concerning LUM/IVA and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

_____
Printed Name

_____ _____
Signature Date