1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

An Exploratory Phase 2, 2-part, Randomized, Double-blind, Placebo-controlled Study With a Long-term, Open-label Period to Explore the Impact of Lumacaftor/Ivacaftor on Disease Progression in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for *F508del*

Vertex Study Number: VX16-809-121

[redacted]

EudraCT Number: 2017-003761-99

Date of Protocol: 24 July 2019 (Version 4.0)

Replaces Version 3.0 (dated 11 June 2018)

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210-1862, USA

2 PROTOCOL SYNOPSIS

Title An Exploratory Phase 2, 2-part, Randomized, Double-blind, Placebo-controlled Study With a Long-term, Open-label Period to Explore the Impact of Lumacaftor/Ivacaftor on Disease Progression in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for *F508del*

Brief Title A Study to Explore the Impact of Lumacaftor/Ivacaftor on Disease Progression in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for *F508del*

Clinical Phase and Clinical Study Type Phase 2, exploratory

Objectives

Primary Objective

To explore the impact of lumacaftor/ivacaftor (LUM/IVA) on disease progression in subjects aged 2 through 5 years with cystic fibrosis (CF), homozygous for *F508del*

Secondary Objective

To explore the relationship between lung clearance index (LCI) and imaging modalities for LUM/IVA in subjects aged 2 through 5 years with CF, homozygous for *F508del*

Endpoints

Primary Endpoint

Absolute change from baseline in magnetic resonance imaging (MRI) global chest score at Week 48

Secondary Endpoints

- Absolute change from baseline in $LCI_{2.5}$ through Week 48
- Absolute change from baseline in weight-for-age z-score at Week 48
- Absolute change from baseline in stature-for-age z-score at Week 48
- Absolute change from baseline in body mass index (BMI)-for-age z-score at Week 48

[redacted]

Number of Subjects	Approximately 50 subjects
Study Population	Male and female subjects 2 through 5 years of age (inclusive) with CF, homozygous for *F508del*
Investigational Drug	Active substance: LUM/IVA fixed-dose combination Activity: CFTR corrector and potentiator (chloride ion [Cl^-] secretion) Strength and route of administration: • LUM 100-mg/IVA 125-mg granules for oral administration • LUM 150-mg/IVA 188-mg granules for oral administration • LUM 100-mg/IVA 125-mg tablets for oral administration LUM/IVA matching placebo Strength and route of administration: LUM 0-mg/IVA 0-mg granules for oral administration
Study Duration	Excluding the Screening Period, the planned study duration is 98 weeks (± 4 days) (from Day 1 to last day of Safety Follow-up Visit).

Study Design

The study includes the following:

- Screening Period (Day -28 through Day -1)
- Treatment Period
  - Part 1 Placebo-controlled Period: Day 1 through Week 48
  - Part 2 Open-label Period: Week 48 through Week 96
- Safety Follow-up Visit (Week 98 [2 weeks ± 4 days after the last dose of study drug])

Subjects will receive LUM 100 mg/IVA 125 mg every 12 hours (q12h) (subjects weighing <14 kg at screening), LUM 150 mg/IVA 188 mg q12h (subjects weighing ≥14 kg at screening), or matching placebo (Part 1 only) during the Treatment Period. No downward dose adjustments will be made if a subject's weight decreases. If a subject subsequently weighs ≥14 kg at 2 consecutive visits, the dose will be adjusted to LUM 150 mg/IVA 188 mg q12h at the second visit where weight is ≥14 kg. Subjects who turn 6 years of age at or after the Week 48 Visit will receive LUM 200 mg/IVA 250 mg q12h (starting at the Week 48 Visit or the next scheduled visit after turning 6 years of age), regardless of weight.

Subjects who prematurely discontinue study treatment will have an Early Termination of Treatment (ETT) Visit as soon as possible.

The Safety Follow-up Visit is required for 1) subjects who complete their ETT Visit <10 days after the last dose of study drug and 2) subjects who interrupt study drug treatment and complete their Week 96 Visit <10 days after the last dose of study drug. 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 study drug treatment at the Week 96 or ETT Visit.

Assessments

Efficacy

MRI, multiple-breath washout (MBW), [redacted], weight, stature, BMI, [redacted]

Safety

Adverse events (AEs), clinical laboratory values, ophthalmologic examinations (OEs), physical examinations, and vital signs

Statistical Analyses

There is limited information on the primary endpoint of MRI global chest score in this specific patient population. Only a small cohort of 17 patients similar to the patient population in this study from Heidelberg, Germany has some relevant information on this perspective. A vague normal prior distribution with a mean of 3.0 and an SD of 1000.0 for the mean change of MRI global chest score from baseline to the end of Year 1 in the placebo arm is used for the Bayesian sample size consideration.

The proposed sample size of 50 subjects (2:1 randomization: 33 LUM/IVA subjects and 17 placebo subjects after adjusting for a dropout rate of 10%) is based on the number of potential subjects expected to be available for participation.

To illustrate potential outcomes, the Bayesian posterior probability that the mean change in the primary endpoint is better in the LUM/IVA group than placebo will be calculated.

For this study, a positive mean change of 3.0 points in the placebo arm (consistent with Heidelberg data) and a common SD of 5.0 in each arm were assumed. In this scenario, a maximum observed positive mean change of approximately 1.66 in the LUM/IVA arm would yield 80% Bayesian posterior probability of LUM/IVA being superior to placebo.

The actual Bayesian posterior probability of LUM/IVA being superior to placebo will be calculated using the actual observed mean change in the LUM/IVA arm and placebo arm at Week 48, which will serve as the primary analysis for this study. The primary endpoint and all secondary [redacted] specified in the protocol will also be analyzed using descriptive summary statistics. The reason for using descriptive summary statistics is due to the limited sample size and the associated insufficient power from the traditional statistical analysis perspective.

The primary endpoint of absolute change in MRI global chest score from baseline at Week 48 will be analyzed using descriptive summary statistics for both between treatment arm difference and within-treatment change.

The secondary [redacted] of absolute change in $LCI_{2.5}$ [redacted] from baseline through Week 48 will also be analyzed using descriptive summary statistics for both between treatment arm difference and within-treatment change. The change from baseline to the average of all post-baseline measures at scheduled visits will be used for this analysis. Additional summary of changes from baseline at each post-baseline time point (at Week 12, Week 24, Week 36, and Week 48 for $LCI_{2.5}$ [redacted] will be provided in a similar way.

[redacted]

Descriptive summary statistics including number of subjects, mean, median, SD, minimum, and maximum, along with the corresponding 95% CIs from the descriptive summary statistics will be provided.

Additional Bayesian summary statistics, including the 95% credible intervals on the primary endpoint of absolute change in MRI global chest score from baseline at Week 48 [redacted], may be explored. Details and analysis for [redacted] safety endpoints, along with the details of statistical analysis will be provided in the statistical analysis plan.

IDMC Reviews

An independent data monitoring committee (IDMC) will conduct safety reviews of study data as outlined in the IDMC charter.

3 SCHEDULE OF ASSESSMENTS

Table 3-1 Study VX16-809-121: Screening

Assessment	Screening Visit Day -28 through Day -1
Informed consent/assent	X
Demographics	X
Medical history	X
Medications review[a]	X
Stature, weight, and vital signs[b,c]	X
OE[d]	X
Full physical examination	X
CFTR genotype[e,f]	X
Serum chemistry[f]	X
Hematology[f]	X
[redacted]	
Sweat chloride[h]	X
MBW[i]	X
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit (if required)

BMI: body mass index; *CFTR*: cystic fibrosis transmembrane conductance regulator gene; [redacted];
ICF: informed consent form; MBW: multiple-breath washout; OE: ophthalmological examination

[a] All medications taken within 28 days before the first dose of study drug through the end of the study will be recorded (Section 9.5).

[b] If children can stand unassisted and follow directions, stature should be measured as height; otherwise, stature will be measured as length. Stature and weight must be measured with shoes off and while wearing light clothing. BMI will be derived from this assessment. Refer to Section 11.5.4 for details.

[c] The subject should rest for at least 5 minutes before having vital signs measured.

[d] An OE will be conducted by a licensed ophthalmologist or optometrist. The examination does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the Screening Visit. Subjects with documentation of bilateral lens removal do not need the OE. Refer to Section 11.5.5 for details.

[e] Subjects without a documented genotype in their medical record will be tested to assess *CFTR* genotype (see inclusion criterion 6 [Section 8.1]).

[f] Refer to Section 11.5.2 for details.

[redacted]

[h] If an eligible historical sweat chloride result is documented in the subject's medical record, that result alone (and not the Screening Visit result) may be used to determine eligibility (see inclusion criterion 5 [Section 8.1]). For subjects using an historical sweat chloride value documented in their medical record to determine eligibility, the sweat chloride test at the Screening Visit is still required. Refer to Section 11.4.3 for details.

[i] The MBW assessment may be performed pre- or post-bronchodilator. The assessment will be performed in multiple replicates as described in the MBW manual. If the subject cannot perform the MBW assessment at the Screening Visit, this assessment may be repeated during the Screening Period. The subject will be considered a screen failure if the MBW assessment cannot be performed (i.e., if 2 technically acceptable MBW tests are not achieved) at the Screening Visit or during re-testing. Refer to Section 11.4.2 for details.

Table 3-2 Study VX16-809-121: Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period									ETT Visit[b]	Safety Follow-up Visit[c]
	Part 1: Placebo-controlled Period				Part 1/ Part 2[d]	Part 2: Open-label Period[e]					
	Day 1	Day 3 (± 1 Day)	Day 15 (± 3 Days)	Weeks 12, 24, 36 (± 7 Days)	Week 48 (± 7 Days)	Day 338[f] (± 1 Day)	Day 350 (± 3 Days)	Weeks 60, 72, 84 (± 7 Days)	Week 96 (± 7 Days)	As Soon as Possible After the Last Dose	2 Weeks (± 4 Days) After the Last Dose
Clinic visit	X		X	X	X		X	X	X	X	X
Telephone contact[g]		X				X					
Randomization[h]	X										
Stature and weight[i]	X		X	X	X		X	X	X	X	X
Vital signs[j]	X[k]		X	X	X[k]		X	X	X	X	X
OE[l]					X[m]				X[m,n]	X[m,n]	X[m,n]
Full PE[o]	X			Week 24	X			Week 72	X	X	X

[a] Assessments will be performed before study drug dosing unless noted otherwise (Section 11.1).

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

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

[d] The first open-label dose of LUM/IVA will be the dose administered at the Week 48 Visit after completion of the predose assessments.

[e] If the subject's Week 48 Visit is delayed, all subsequent visits must be delayed accordingly based on the actual Week 48 Visit date.

[f] The Day 338 Visit (telephone contact) should occur 1 to 3 days after the actual date of the Week 48 Visit, regardless of whether it is Study Day 338.

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

[h] Randomization must only occur after all inclusion and exclusion criteria are met and before the first dose of study drug. Randomization will be done through IWRS and may occur on Day -1.

[i] If children can stand unassisted and follow directions, stature should be measured as height; otherwise, stature will be measured as length. Stature and weight must be measured with shoes off and while wearing light clothing. BMI will be derived from this assessment. Refer to Section 11.5.4 for details.

[j] The subject should rest for at least 5 minutes before having vital signs measured (Section 11.5.4).

[k] Vital signs will be measured predose and at 1 hour (± 15 minutes), 2 hours (± 15 minutes), and 4 hours (± 15 minutes) postdose on Day 1 and at Week 48.

[l] An OE will be conducted by a licensed ophthalmologist or optometrist. Subjects with documentation of bilateral lens removal do not need the OE. Refer to Section 11.5.5 for details.

[m] Subjects may complete the OE up to 7 days before the scheduled visit.

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

[o] Symptom-directed PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

Table 3-2 Study VX16-809-121: Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period: Part 1: Placebo-controlled Period: Day 1	Part 1: Placebo-controlled Period: Day 3 (± 1 Day)	Part 1: Placebo-controlled Period: Day 15 (± 3 Days)	Part 1: Placebo-controlled Period: Weeks 12, 24, 36 (± 7 Days)	Part 1/ Part 2[d]: Week 48 (± 7 Days)	Part 2: Open-label Period[e]: Day 338[f] (± 1 Day)	Part 2: Open-label Period[e]: Day 350 (± 3 Days)	Part 2: Open-label Period[e]: Weeks 60, 72, 84 (± 7 Days)	Part 2: Open-label Period[e]: Week 96 (± 7 Days)	ETT Visit[b]: As Soon as Possible After the Last Dose	Safety Follow-up Visit[c]: 2 Weeks (± 4 Days) After the Last Dose
Abbreviated PE	X[p]				X[p]						
Serum chemistry[q,r]	X		X	X	X		X	X	X	X	X
Hematology[q,r]				X	X			X	X	X	X
[redacted]											
MBW[v]	X			X	X			X	X	X	X
MRI	X[w]				X[w,x]				X[w,w]	X	

[p] An abbreviated PE will be performed 4 hours (± 30 minutes) postdose on Day 1 and at Week 48 (Section 11.5.4).

[q] Refer to Section 11.5.2 for details.

[r] If the MRI occurs before the scheduled study visit, this assessment may occur on the same day as the MRI assessment. Blood draws performed on the same day as the MRI assessment must be collected before administration of any medications related to MRI procedures.

[redacted]

[v] The MBW assessment should be performed pre-bronchodilator and before dosing. The assessment will be performed in multiple replicates. Refer to Section 11.4.2 for details.

[w] Subjects may complete the imaging assessment up to 7 days before the scheduled visit. Screening assessments must be completed, inclusion and exclusion criteria must be reviewed, and subjects must meet eligibility criteria relevant at the time before participating in the baseline MRI assessment up to 7 days before Day 1. If the MRI is performed before the scheduled visit, the blood draws for serum chemistry, hematology, and [redacted] may be performed on the day of the MRI assessment. Blood draws for any assessment performed on the same day as MRI testing must be collected before administration of any medications related to MRI procedures. [redacted]

[x] The MRI at Weeks 48 and/or 96 may be delayed for up to 60 days if the subject is recovering from a PEx. The MRI should be done after the PEx is resolved and at least 28 days after the last dose of the antibiotic regimen for the treatment of pulmonary infection has been completed. If the 28-day antibiotic-free period is not completed before the 60-day extension ends, the MRI should be completed within 1 week of the end of the 60-day extension. If the MRI at Weeks 48 and/or 96 is delayed, all other assessments must also be delayed.

Table 3-2 Study VX16-809-121: Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period									ETT Visit[b]	Safety Follow-up Visit[c]
	Part 1: Placebo-controlled Period				Part 1/ Part 2[d]	Part 2: Open-label Period[e]					
	Day 1	Day 3 (± 1 Day)	Day 15 (± 3 Days)	Weeks 12, 24, 36 (± 7 Days)	Week 48 (± 7 Days)	Day 338[f] (± 1 Day)	Day 350 (± 3 Days)	Weeks 60, 72, 84 (± 7 Days)	Week 96 (± 7 Days)	As Soon as Possible After the Last Dose	2 Weeks (± 4 Days) After the Last Dose
[redacted]											
Study drug dosing[z]	LUM/IVA q12h or placebo q12h				LUM/IVA q12h						
Observation 4 hours after the first dose	X				X						
Study drug count	X		X	X	X		X	X	X	X	
Medications, treatments, and procedures review	Continuous from signing of ICF through Safety Follow-up Visit (if required)										
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit (if required)										

AE: adverse event; BMI: body mass index; ETT: Early Termination of Treatment; [redacted]; ICF: informed consent form; [redacted]; IVA: ivacaftor; IWRS: interactive web response system; LUM: lumacaftor; MBW: multiple-breath washout; MRI: magnetic resonance imaging; OE: ophthalmological examination; PE: physical examination; [redacted]; q12h: every 12 hours

[redacted]

z Study drug will be administered q12h (± 2 hours) within 30 minutes of consuming fat-containing food. On days of scheduled visits, the dose will be administered at the site after predose assessments have been completed. Refer to Section 9.6 for details. If the Treatment Period has been extended to allow for recovery from a PEx and the Week 48 and/or Week 96 Visit is delayed (Section 11.1), subjects should continue to take study drug until the Week 48 and/or Week 96 Visit has been completed.

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List of Abbreviations

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
BMI z-score	BMI-for-age z-score; BMI, adjusted for age and sex
CF	cystic fibrosis
CFTR	*CF transmembrane conductance regulator* gene
CFTR	CF transmembrane conductance regulator protein
CI	confidence interval
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DZL	Deutsches Zentrum fur Lungenforschung
EDC	electronic data capture
EENT	eyes, ears, nose, throat
EMA	European Medicines Agency
ETT	Early Termination of Treatment
EU	European Union
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F508del	CFTR protein lacking the phenylalanine normally found at position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
[redacted]	[redacted]
FEV1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
Gd	Gadolinium
GGT	gamma-glutamyl transferase
GPS	Global Patient Safety
height z-score	height-for-age z-score; height, adjusted for age and sex
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IPD	important protocol deviation
IRB	institutional review board
[redacted]	[redacted]
IV	intravenous
IVA	ivacaftor
IWRS	interactive web response system
K-M	Kaplan-Meier
LCI	lung clearance index

Abbreviation	Term
$LCI_{2.5}$	the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value
[redacted]	
LFT	liver function test
LS	least squares
LUM	lumacaftor
MBW	multiple-breath washout
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures
MRI	magnetic resonance imaging
OE	ophthalmological examination
P	probability
pbo	placebo
PE	physical examination
PEx	pulmonary exacerbation
PI	pancreatic insufficiency
PK	pharmacokinetic, pharmacokinetics
PT	Preferred Term
q12h	every 12 hours
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	System Organ Class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
UTE	ultrashort echo time
weight z-score	weight-for-age z-score; weight, adjusted for age and sex

5 INTRODUCTION

5.1 Background

Cystic fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality and at present, there is no cure. CF affects approximately 70,000 individuals worldwide,[1] with approximately 30,000 individuals in the US,[1, 2] 32,000 individuals in the EU,[3] 4,100 individuals in Canada,[4] and 3,200 individuals in Australia.[5] Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is approximately 40 years.[2, 6, 7] Although the disease affects multiple organs, progressive loss of lung function is the leading cause of mortality.[8]

CF is caused by a defect in the gene encoding CFTR, an epithelial chloride (Cl^-) ion channel that is responsible for aiding in the regulation of salt and water absorption and secretion in various tissues.[9] This function is defective in patients with CF due to a loss of cell surface expression and/or function of CFTR.

Lumacaftor (LUM; VX-809)/ivacaftor (IVA; VX-770) combination therapy (Orkambi) is the first medicine designed to treat the underlying molecular defect and enhance the function of CFTR in patients homozygous for *F508del*. Orkambi is approved in the US, Canada, and EU for patients 2 years and older who are homozygous for *F508del*, in Switzerland, Liechtenstein, and Australia for patients 6 years and older who are homozygous for *F508del*, and in Israel for patients 12 years and older who are homozygous for *F508del*. The LUM/IVA development program is designed to support the hypothesis that an oral chronic treatment restoring CFTR function can lead to improved pulmonary and extrapulmonary manifestations of CF, prevent progressive lung damage, and ultimately prolong survival.

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

5.2 Study Rationale

CF greatly affects the pediatric population, as approximately half of the total CF population is less than 18 years of age.[10] Even before the widespread adoption of newborn screening, the majority of patients with CF were diagnosed in infancy or early childhood due to manifestations of the disease. Pancreatic destruction leading to pancreatic exocrine insufficiency begins in utero, and lung involvement is manifest by pulmonary inflammation and infection that begins shortly after birth.

Pharmacokinetic (PK) and preliminary safety profiles for LUM/IVA combination therapy have been established in subjects 2 through 5 years of age who are homozygous for *F508del* (Study VX15-809-115 [Study 115] Part A [completed] and Part B [ongoing]). The present study is designed to explore long-term disease progression and efficacy of LUM/IVA in subjects 2 through 5 years of age, homozygous for *F508del*. The long-term data will provide information about disease progression and the potential for disease modification by early CFTR-targeted intervention and will support the efficacy and safety of LUM/IVA in this younger CF population.

6 STUDY OBJECTIVES

6.1 Primary Objective

To explore the impact of LUM/IVA on disease progression in subjects aged 2 through 5 years with CF, homozygous for *F508del*

6.2 Secondary Objective

To explore the relationship between lung clearance index (LCI) and imaging modalities for LUM/IVA in subjects aged 2 through 5 years with CF, homozygous for *F508del*

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Absolute change from baseline in magnetic resonance imaging (MRI) global chest score at Week 48

7.2 Secondary Endpoints

- Absolute change from baseline in $LCI_{2.5}$ through Week 48
- Absolute change from baseline in weight-for-age z-score at Week 48
- Absolute change from baseline in stature-for-age z-score at Week 48
- Absolute change from baseline in body mass index (BMI)-for-age z-score at Week 48

[redacted]

[redacted]

8 STUDY POPULATION

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

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

8.1 Inclusion Criteria

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

     AND
   - clinical manifestations of CF.
6. Subjects who are homozygous for *F508del* (genotype to be confirmed at the Screening Visit or as documented in the subject's medical record).
7. Subjects with stable CF disease as deemed by the investigator at the Screening Visit.
8. Subjects who are willing to remain on a stable CF medication regimen through the Safety Follow-up Visit, if applicable.

8.2 Exclusion Criteria

1. History of any illness or comorbidity reviewed at the Screening Visit that, in the opinion of the investigator, might confound the results of the study, interfere with or pose an additional risk in conducting the study assessments, or pose an additional risk in administering study drug to the subject. For example, a history of cirrhosis with portal hypertension, or prior allergic reaction to gadolinium (Gd)-based contrast material, or metallic implants incompatible with MRI.
2. Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject (as deemed by the investigator).
3. Any of the following abnormal laboratory values at the Screening Visit:
   - Hemoglobin <10 g/dL
   - Alanine transaminase (ALT), aspartate transaminase (AST), or total bilirubin >2 × upper limit of normal (ULN)
   - Abnormal renal function defined as glomerular filtration rate ≤45 mL/min/1.73 m^2 (calculated by the Bedside Schwartz equation)[11]
4. An acute upper or lower respiratory infection, PEx as defined by the investigator, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug).
5. Any clinically significant "non-CF-related" illness within 2 weeks before Day 1. "Illness" is defined as an acute (serious or nonserious) condition (e.g., gastroenteritis).
6. History of solid organ or hematological transplantation.
7. Ongoing or prior participation in an investigational drug study (including studies investigating LUM and/or IVA) within 30 days of the Screening Visit.
   - A washout period of 5 terminal half-lives of the previous investigational study drug, or 30 days, whichever is longer, must elapse before the Screening Visit.
   - The duration of the elapsed time may be longer if required by local regulations.

   Note: Ongoing participation in a noninterventional study (including observational studies) is permitted.
8. Use of restricted medication or food within specified duration before the first dose of study drug as defined in Section 9.4.
9. Inability of the subject to perform the multiple-breath washout (MBW) assessment during the Screening Period (Section 11.4.2).
10. History of cataract/lens opacity or evidence of cataract/lens opacity determined to be clinically significant by a licensed ophthalmologist during the ophthalmologic examination (OE) at the Screening Visit. The Screening Visit OE does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the Screening Visit. Subjects with documentation of bilateral lens removal do not need the OE and this criterion does not apply.

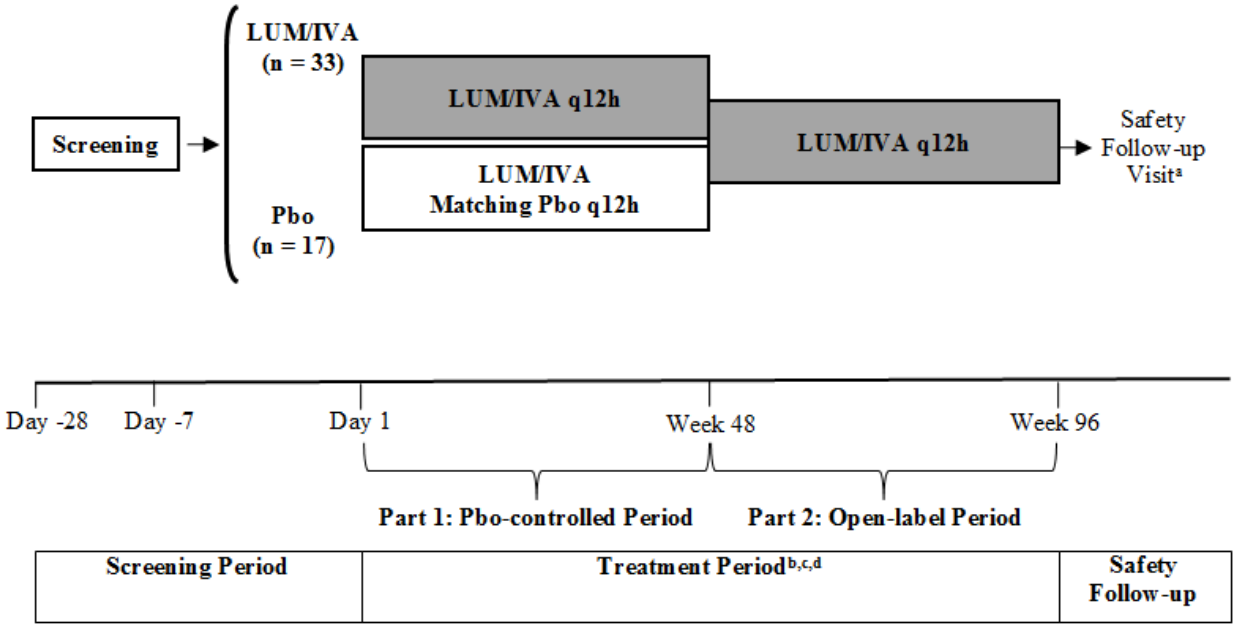
11. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study.

9 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 2, 2-part, randomized, double-blind, placebo-controlled, parallel-group study with a long-term open-label period in subjects 2 through 5 years of age with CF, homozygous for *F508del* (Figure 9-1).

Figure 9-1 VX16-809-121 Study Design



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

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

[b] Approximately 50 subjects are planned to be randomized (2:1) to receive LUM/IVA or placebo. Subjects will receive LUM 100 mg/IVA 125 mg every 12 hours (q12h) (subjects weighing <14 kg at screening), LUM 150 mg/IVA 188 mg q12h (subjects weighing ≥14 kg at screening), or matching placebo (Part 1 only) during the Treatment Period.

[c] No downward dose adjustments will be made if a subject's weight decreases. If a subject subsequently weighs ≥14 kg at 2 consecutive visits, the dose will be adjusted to LUM 150 mg/IVA 188 mg q12h, at the second visit where weight ≥14 kg. Subjects who turn 6 years of age at or after the Week 48 Visit will receive LUM 200 mg/IVA 250 mg q12h (starting at the Week 48 Visit or the next scheduled visit after turning 6 years of age), regardless of weight.

[d] Subjects who prematurely discontinue study treatment will have an ETT Visit as soon as possible.

9.1.1 Screening

Screening Visit assessments are listed in Table 3-1.

Screening will occur within 28 days before administration of study drug. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from each subject's parent or legal guardian and the subject must sign an assent form (if applicable) before any study-specific procedures can be performed. The ICF (and assent form, if applicable) will comply with all applicable regulations governing the protection of human subjects and will be approved by Vertex and the site's institutional review board (IRB).

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

9.1.1.1 Repetition of Screening Assessments

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

- If the subject cannot complete the MBW assessment (Section 11.4.2).
- If there is clear evidence of a laboratory error (e.g., hemolyzed sample), equipment malfunction, or technician error, collection of a repeat sample for the appropriate laboratory test may be permitted after discussion with the Vertex medical monitor or authorized designee.
- Exclusionary liver function test (LFT) levels, which may be retested within 14 days of the original Screening Visit date.

In these cases, the individual assessment may be repeated during the Screening Period without repeating all the other Screening Visit assessments. Repetition of these screening assessments will not reset Screening Period window dates; however the Screening Period window may be extended by 1 week after approval by the medical monitor or authorized designee (Section 9.1.1.3). If repeat values of the individual assessment(s) are within the eligibility criteria and completed within the Screening Period window, then the subject is eligible for the study.

9.1.1.2 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 and the OE (if performed within the last 3 months before the Screening Visit). For assessments listed in Section 9.1.1.1, the individual assessment may be repeated during the Screening Period without repeating all the other Screening Visit assessments.

Subjects may only be rescreened once for entry into Part 1. If a subject is rescreened, the new screening window date will begin once the first rescreening assessment has been initiated.

9.1.1.3 Extension of Screening Period Window

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

- Repetition of the Screening Period assessments (Section 9.1.1.1)
- To account for exclusionary events that may not reflect the subject's true baseline due to an acute event, which may resolve
- Scheduling of OE (Section 11.5.5)
- Availability or malfunction of required equipment, or technician error.

9.1.2 Treatment Period

The Treatment Period is 96 weeks; study drug will be administered every 12 hours (q12h) from Day 1 through Week 96 (Section 9.1). The Treatment Period can be extended up to 60 days in the event of a PEx: up to 60 days for the Week 48 MRI, and up to 60 days for the Week 96 MRI, for a total of up to 120 days. Antibiotics taken for a pulmonary infection or exacerbation must be completed at least 28 days before the MRI scan (Section 11.1). If the 28-day antibiotic free period is not completed before the 60-day extension ends, the MRI should be completed within 1 week of the end of the 60-day extension. If the MRI at Weeks 48 and 96 is delayed, all other assessments must also be delayed.

Study visits during the Treatment Period will occur as shown in Table 3-2. Subjects will be outpatients during the Treatment Period.

Study drug administration and management details are provided in Section 9.6 and Section 10, respectively.

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

9.1.3 Follow-up

Subjects will have a Safety Follow-up Visit 2 weeks (± 4 days) after the last study drug dose. Safety Follow-up Visit assessments are listed in Table 3-2.

The Safety Follow-up Visit is required for 1) subjects who complete their Early Termination of Treatment (ETT) Visit <10 days after the last dose of study drug (Section 9.1.4) and 2) subjects who interrupt study drug treatment and complete their Week 96 Visit <10 days after the last dose of study drug; it is not required for subjects who continue onto commercially available, physician-prescribed LUM/IVA within 2 weeks (± 4 days) of completing study drug treatment at the Week 96 or ETT Visit.

9.1.4 Early Termination of Treatment Early Discontinuation

If the subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. Subjects who prematurely discontinue treatment may also be required to complete the Safety Follow-up Visit, approximately 2 weeks (± 4 days) after their last dose of study drug (Section 9.1.3). The assessments performed at the Safety Follow-up Visit are listed in Table 3-2.

If the ETT Visit occurs ≥10 days following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

Subjects who prematurely discontinue study drug treatment for adverse events (AEs) should be followed until the AE is considered resolved.

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

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

9.1.5 Independent Data Monitoring Committee

Safety and tolerability data will be reviewed by an independent data monitoring committee (IDMC) with the primary goal of evaluating the safety of the study drug regimen to ensure the safety of the subjects in the study (Section 12.3.5.2). Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be included in the IDMC charter. The IDMC charter will be finalized before the first subject is enrolled.

9.2 Method of Assigning Subjects to Treatment Groups

Part 1

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

Part 2

Part 2 is open-label. Randomization is not required for Part 2 because all subjects will receive LUM/IVA.

9.3 Rationale for Study Design and Study Drug Regimens

9.3.1 Study Design

CF is a rare, inherited genetic disease that is life-shortening and seriously debilitating, for which there is no cure. CF is caused by a reduction or loss of CFTR activity, with production of highly viscous mucus and reduced mucociliary clearance in the lungs clogging the airways and promoting inflammation and infection, causing continued lung function decline over time. CF pulmonary disease, the major driver of morbidity and mortality in CF, manifests early and progresses throughout life. However, it is not uncommon for young patients with CF to have well-preserved or even normal lung function as measured by spirometry.[12-15] In patients younger than 6 years of age, it is also very challenging to measure lung function using spirometry, and results are variable. However, through use of imaging techniques (non-invasive and invasive) and MBW assessments, it has been shown that patients in this age group with severe CF-causing mutations are likely to already have pulmonary structural aberrations and functional abnormalities.[14, 16-22]

Vertex has established efficacy, safety, and PK profiles for LUM/IVA combination therapy in subjects 6 years of age and older, homozygous for *F508del* (Studies VX12-809-103,

VX12-809-104, VX12-809-105, VX13-809-011, and VX14-809-109). In addition, safety and PK profiles for LUM/IVA combination therapy have been established in subjects 2 through 5 years of age, homozygous for *F508del* (Study VX15-809-115 [Study 115]). The present study is designed to explore efficacy and to obtain safety information in a very young pediatric population in a placebo-controlled setting, with a window of opportunity to halt disease progression and prevent organ damage by early intervention with therapies that treat the underlying cause of CF. The impact of LUM/IVA on lung function will be explored using 2 methods:1) thoracic MRI, an imaging assessment used to determine structural and functional lung abnormalities and to monitor disease progression, and 2) LCI, a measure of ventilation inhomogeneity that is based on tidal breathing techniques that have been evaluated in patients as young as infants.

Given the intent to try to demonstrate efficacy with respect to MRI chest score and LCI, which are still endpoints under evaluation in this age group, the use of placebo in Part 1 (48-week Placebo-controlled Period) is necessary in order to provide a robust assessment. It is considered justified since all subjects within the relevant country are expected to be recruited before LUM/IVA is approved in this age group or is available commercially. The placebo or active drug will be added to subject's current standard of care, and no therapies are required to be withdrawn. Therefore, no subject will be considered disadvantaged by the use of placebo, and all will have the potential to benefit in the rollover study when they will receive LUM/IVA. Furthermore, this study is randomized 2:1, with twice as many subjects being on active therapy.

Exploration of the efficacy of LUM/IVA over the course of Part 2 (48-week Open-label Period) in this younger CF population will continue to provide information about disease progression and the potential for disease modification by early CFTR-targeted intervention.

9.3.2 Study Drug Dose and Duration

9.3.2.1 Dose of LUM/IVA

Subjects will be randomized 2:1 to receive LUM/IVA or placebo. The dose regimens of LUM 100 mg/IVA 125 mg q12h (subjects weighing <14 kg at screening) and LUM 150 mg/ IVA 188 mg q12h (subjects weighing ≥14 kg at screening) were chosen based on Study 115A, a safety and PK study of LUM/IVA in subjects 2 through 5 years of age, and an interim analysis of confirmatory PK data obtained during Study 115B. Subjects who turn 6 years of age at or after the Week 48 Visit will receive LUM 200 mg/IVA 250 mg q12h (starting at the Week 48 Visit or the next scheduled visit after turning 6 years of age), regardless of weight.

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

9.3.2.2 Duration of Dosing

The duration of 48 weeks of placebo-controlled treatment in Part 1, plus an additional 48 weeks of open-label LUM/IVA treatment in Part 2, will provide an adequate assessment of efficacy and safety, including long-term impact on disease progression, in particular, structural damage assessed via MRI. If the Treatment Period has been extended to allow for recovery from a PEx and the Week 48 and/or Week 96 Visit is delayed, subjects should continue to take study drug until the Week 48 and/or Week 96 Visit has been completed.

9.3.3 Rationale for Study Assessments

The following efficacy assessments are standard assessments used in studies in the LUM/IVA development program: weight, stature, BMI, [redacted] Rationale is provided below for the following efficacy assessments: MRI, MBW for the measurement of LCI, [redacted]

MRI Assessment: Current imaging technologies have demonstrated potential advantages in the evaluation of early lung disease in infants and children with CF. MRI with perfusion provides greater sensitivity than computerized tomography (CT) scan for imaging mucous plugging and bronchial wall thickening without ionizing radiation exposure and offers an accepted scoring system. It is recognized that MRI with ultrashort echo time (UTE) may be more sensitive for bronchiectasis than conventional sequences. However, MRI with perfusion is an accepted technique that is currently used by the DZL Clinical Network in the clinical care of patients with CF with an established, standard, and published protocol, to evaluate lung function and morphology, diagnose abnormalities, and to monitor disease progression on an annual basis. Data suggest Gd uptake in the brain after repeated use, thus the EMA restrictions.[23] However, there is currently no evidence that Gd deposition has caused any harm and EMA has recommended restrictions for some agents to prevent any risks that could potentially be associated with Gd brain deposition.

A recent analysis from an exploratory imaging substudy in Study VX14-809-109, UTE MRI was demonstrated to be a feasible approach for detecting the effect of LUM/IVA in subjects 6 through 11 years of age with CF, despite the small sample size, short duration of treatment, and limitations in image quality. Furthermore, several studies have demonstrated the application of MRI for non-invasive monitoring of early CF lung disease in patients including infants and young children. For example, recent studies demonstrated: 1) that MRI was able to detect abnormalities in lung structure and perfusion, as well as response to treatment for PExs in infants and preschool children with CF[22]; 2) use of an MR-scoring system that can be used in routine assessment of lung disease in CF patients, including infants and young children[24]; 3) UTE MRI detected structural lung disease in young CF patients, with imaging data that was well-correlated with CT[25]; and 4) that MRI and MBW may serve as complementary assessments for non-invasive monitoring and as quantitative endpoints in trials in children with CF.[26]

MBW Assessment: LCI will be derived from MBW testing. LCI is a measure of ventilation inhomogeneity that is based on tidal breathing techniques that have been evaluated in patients as young as infants.[27, 28] Studies have shown that LCI correlates with forced expiratory volume in 1 second (FEV_1) in its ability to measure airway disease in patients with mild to moderate lung disease, but can also detect lung disease at an earlier stage than spirometry.[20, 21] Furthermore, data from Study VX10-770-106 in subjects with CF with an FEV_1 >90% showed LCI to be a more sensitive outcome measure than FEV_1. LCI has also been shown to be a sensitive measure of lung function in subjects aged 6 to 11 years with high baseline lung function treated with LUM/IVA combination therapy, as shown by the results of Studies VX14-809-109 and VX13-809-011B, and has demonstrated that early intervention with LUM/IVA can improve lung function in the pediatric CF population. Given the potential advantages of a more sensitive measurement during the early stages of disease progression, $LCI_{2.5}$ will be used as a secondary endpoint in this study. $LCI_{2.5}$ (the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value) represents the most commonly used MBW

parameter.[29] [redacted]

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. OE assessments were added as part of safety monitoring.

OEs: A juvenile rat toxicity study performed to support dosing of IVA in subjects <2 years of age demonstrated lens opacities in some animals.[32] Prior studies in rats and dogs of older age did not demonstrate similar findings.[32] 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 do not suggest an association between IVA treatment and cataract development; however, a potential association has not been fully excluded.

9.4 Study Restrictions

Study restrictions are summarized in Table 9-1.

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

Table 9-1 Study Restrictions

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

CYP: cytochrome P450
Note: The use of restricted medication in subjects with a medical need will be addressed on a case-by-case basis with the medical monitor or authorized designee.
[a] See Section 9.5 for guidance for concomitant medications.

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

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

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

9.5 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.
- Information about bronchodilator use during the study will be collected and documented in the subject's source documents. Subjects who are using a bronchodilator should have their MBW assessments performed according to the guidelines provided in Section 11.4.2.

9.6 Administration

On Day 1 through the Week 96 Visit (last dose of study drug), granules will be orally administered with the approved foods and liquids listed in the study manual (e.g., apple sauce), as shown in Table 9-2. Subjects who turn 6 years of age at or after the Week 48 Visit will be orally administered tablets as shown in Table 9-2.

Table 9-2 Study Drug Administration

Treatment Arm	Time	LUM/IVA (Number of Stick Packs/Tablets)	Placebo (Number of Stick Packs)
LUM/IVA (Part 1)			
Subject screening weight <14 kg[a]	AM	1 stick pack	None
LUM 100 mg/IVA 125 mg q12h	PM	1 stick pack	None
Subject screening weight ≥14 kg[a]	AM	1 stick pack	None
LUM 150 mg/IVA 188 mg q12h	PM	1 stick pack	None
Placebo (Part 1 Only)			
LUM/IVA matching placebo	AM	None	1 stick pack
	PM	None	1 stick pack
LUM/IVA (Part 2)			
Subject <6 years of age and screening weight <14 kg[a]	AM	1 stick pack	NA
LUM 100 mg/IVA 125 mg q12h	PM	1 stick pack	NA
Subject <6 years of age and screening weight ≥14 kg[a]	AM	1 stick pack	NA
LUM 150 mg/IVA 188 mg q12h	PM	1 stick pack	NA
Subjects ≥6 years of age[b]	AM	2 tablets	NA
LUM 200 mg/IVA 250 mg q12h	PM	2 tablets	NA

IVA: ivacaftor; LUM: lumacaftor; NA: not applicable; q12h: every 12 hours

[a] Doses are based on the subject's weight at screening. No downward dose adjustments will be made if a subject's weight decreases. If a subject subsequently weighs ≥14 kg at 2 consecutive visits, the dose will be adjusted to LUM 150 mg/IVA 188 mg q12h at the second visit where weight ≥14 kg.

[b] Subjects who turn 6 years of age at or after the Week 48 Visit will receive LUM 200 mg/IVA 250 mg q12h (starting at the Week 48 Visit or the next scheduled visit after turning 6 years of age), regardless of weight.

Study drug 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 study drug (morning and evening, as applicable) should be administered at approximately every 12 hours (± 2 hours) on each dosing occasion (e.g., if the morning dose is administered at 08:00 on Day 1, all subsequent morning doses should be administered between 06:00 and 10:00).
2. The granule formulation will be dispensed by opening the stick packs containing the granules and mixing the granules with the approved foods and liquids listed in the study manual (e.g., apple sauce). Each dose will be comprised of the approved food or liquids into which the granules from the stick packs are mixed. Details on preparing study drug will be provided in the pharmacy manual.
3. On the Day 1 and Week 48 Visits, all subjects will be observed for 4 hours after the first dose.
4. On days of scheduled visits, with the exception of afternoon visits addressed below, the morning dose will be administered at the site after predose assessments have been completed.

5. If a subject's scheduled visit is to occur in the afternoon, the following guidelines must be used for administering either the morning or evening dose:
    - If the dose in the clinic will be within 6 hours of the subject's scheduled morning 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 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/caregivers will be instructed to bring all used and unused study drug materials to the site; study drug will be dispensed at each visit, as appropriate.
7. If the Treatment Period has been extended to allow for recovery from a PEx and the Week 48 and/or Week 96 Visit is delayed (Section 11.1), subjects should continue to take study drug until the Week 48 and/or Week 96 Visit has been completed.

9.7 Dose Modification for Toxicity

If any unacceptable toxicity arises, individual subjects will discontinue dosing (Section 9.1.4).

9.8 Removal of Subjects

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

Subjects who discontinue study treatment early should return for study assessments at the ETT and Safety Follow-up Visits, if applicable, as noted in Section 9.1.3 and Section 9.1.4.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit, if applicable (see Section 9.1.4), and follow up with the subject regarding any unresolved AEs.

If the subject 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 withdraws from the study, the study data and samples collected will remain part of the study. A subject will not be able to request the withdrawal of his/her information from the study data. A subject may request destruction of the samples collected from him/her during the study as long as those samples can be identified as his/her samples.

9.9 Replacement of Subjects

Subjects who withdraw or are withdrawn during the study drug treatment period(s) will not be replaced.

10 STUDY DRUG INFORMATION AND MANAGEMENT

10.1 Preparation and Dispensing

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

10.2 Packaging and Labeling

Vertex will supply the granules in stick packs in kits and LUM 100-mg/IVA 125-mg tablets in child-resistant weekly blister cards. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for study drug will be included in the Pharmacy Manual.

10.3 Study Drug Supply, Storage, and Handling

Packaging and storage conditions for study drug are described in Table 10-1. 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.

Table 10-1 Study Drug

Drug Name	Formulation/ Route	Packaging (Formulation Strength)	Storage Condition
LUM/IVA	Granules/ Oral	Supplied as 100-mg LUM/125-mg IVA granules in **1** stick pack	Store at ≤25°C (77°F) with excursions to 30°C (86°F)
LUM/IVA	Granules/ Oral	Supplied as 150-mg LUM/188-mg IVA granules in **1** stick pack	Store at ≤25°C (77°F) with excursions to 30°C (86°F)
LUM/IVA matching placebo	Granules/ Oral	Supplied as and 0-mg LUM/0-mg IVA granules in **1** stick pack	Store at ≤25°C (77°F) with excursions to 30°C (86°F)
LUM/IVA	Fixed-dose tablet/ Oral	Supplied as 100-mg LUM/125-mg IVA tablets	Store at ≤25ºC (77ºF) with excursions to 30ºC (86ºF)

IVA: ivacaftor; LUM: lumacaftor

10.4 Drug Accountability

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

10.5 Disposal, Return, or Retention of Unused Drug

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

10.6 Compliance

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

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

10.7 Blinding and Unblinding

10.7.1 Blinding

Part 1 is a double-blind study. The subjects/caregivers and all site personnel, including the investigator and the study monitor, and the Vertex study team will remain blinded to treatment assignments until database lock for Part 1 (i.e., database lock for data up to and including the Week 48 Visit) with the following exceptions:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy serious adverse event (SAE) processing and reporting regulations
- Unblinded statistician preparing the final (production) randomization list, who is not part of the study team
- Vertex Clinical Operations IWRS management
- Vertex Clinical Supply Chain
- Vertex medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time
- Subjects and their parent/caregiver should not be informed of their study-related LCI, [redacted], and imaging results during Part 1 and Part 2 of the study regardless if the subject has prematurely discontinued treatment.

<u>Imaging Data Blinding</u>

Despite treatment blinding, knowledge of the imaging data has the potential to suggest whether a subject has been administered active study drug or matching placebo. Therefore, during the conduct of Part 1 (i.e., up to and including the Week 48 Visit), the Vertex study team will have

no access to the postdose imaging data. The central reader of these data will only send the blinded files (no treatment group, with real values for baseline, but with dummy values for all the assessments after baseline) to Vertex to be used for developing the statistical programs.

LCI Data Blinding

Despite treatment blinding, knowledge of the LCI results has the potential to suggest whether a subject has been administered active study drug or matching placebo. Therefore, during the conduct of Part 1 (i.e., up to and including the Week 48 Visit), the Vertex study team will have no access to the post first-dose LCI data. The central reader of these data will only send the blinded files (no treatment group, with real values for screening and baseline for LCI, but with dummy data for LCI for all the assessment values after baseline) to Vertex to be used for developing the statistical programs.

[redacted]

10.7.2 Unblinding

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

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

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

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

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

Vertex GPS or designee will also unblind any SAE reports in compliance with regulatory reporting requirements. In addition, Vertex may, for matters relating to safety concerns, unblind individual subjects at any time.

11 ASSESSMENTS

11.1 Timing of Assessments

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

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

1. Vital signs should be performed before any other procedures that may affect heart rate (e.g., blood draws).

[redacted]

3. The MRI assessment may be performed up to 7 days before the scheduled visit. If the MRI assessment is performed before the scheduled visit, blood draws for serum chemistry, hematology, [redacted] may be performed on the day of the MRI assessment. Blood draws for any assessment performed on the same day as MRI testing must be collected before administration of any medications related to MRI procedures. [redacted]
    - The MRI at Weeks 48 and/or 96 may be delayed for up to 60 days if the subject is recovering from a PEx. The last dose of the antibiotic regimen for the treatment of pulmonary infection or exacerbation must be completed at least 28 days before the MRI. If the 28-day antibiotic-free period is not completed before the 60-day extension ends, the MRI should be completed within 1 week of the end of the 60-day extension. If the MRI at Weeks 48 and/or 96 is delayed, all other assessments must also be delayed.

11.2 Subject and Disease Characteristics

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

Medical history will be elicited from each subject's caregiver during screening. Based on the medical history, the subject will be assessed for any disqualifying medical conditions as

specified in the inclusion and exclusion criteria. The medical history should include a complete review of systems, past medical and surgical histories, and any known allergies.

11.3 Pharmacokinetics

Not applicable.

11.4 Efficacy

11.4.1 MRI With Perfusion

The proposed morpho-functional MR-scoring-system is reproducible and applicable for semi-quantitative evaluation of a large spectrum of CF lung disease severity. Data from a study conducted by the DZL network show that MRI detected abnormalities in lung structure and perfusion, and response to therapy for exacerbations in infants and preschool children with CF. These results support the development of MRI for non-invasive monitoring and as an endpoint in interventional trials for early CF lung disease. This scoring-system is being used routinely in the assessment of CF lung disease and as an endpoint for clinical trials by the DZL network and other CF Centers in Europe.[22, 24]

Children will be sedated according to the established sedation procedure used for diagnostic procedures at each site, such as oral or rectal chloral hydrate (100 mg/kg body weight, maximum dose of 2 g) (± phenobarbital) or propofol, and monitored during the MRI examination by MR-compatible pulse oximetry.

Detailed procedures for the assessment will be provided in the Imaging Manual.

11.4.2 Multiple-breath Washout

Screening Period

Subjects must complete the MBW assessment during the Screening Period. If a subject cannot perform the MBW assessment at the Screening Visit, this assessment may be repeated during the Screening Period (without repeating the other assessments required during the Rescreening Visit). The subject will be considered a screen failure if the MBW assessment cannot be performed (i.e., if 2 technically acceptable tests are not achieved) during the Screening Visit or during re-testing. During the Screening Period, the MBW test may be performed pre- or post-bronchodilator.

Treatment Period

At all visits after the Screening Period, MBW tests should be performed pre-bronchodilator. Each MBW will be performed in multiple replicates at each visit according to the MBW manual.

LCI will be derived from MBW testing. $LCI_{2.5}$ represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value, [redacted]

The mean LCI value at each visit will be calculated using all technically acceptable replicates. All LCI replicate values will be provided by a central reader; however, the LCI central reader will not perform the calculation for the mean LCI values at visits. The mean LCI value at each Treatment Period Visit will be calculated by the sponsor or sponsor designee from the technically acceptable values provided by the LCI central reader.

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

[redacted]

11.4.4 Weight, Stature, and BMI

See Section 11.5.4.

[redacted]

[redacted]

11.5 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, physical examinations (PEs), and OEs.

11.5.1 Adverse Events

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

11.5.2 Clinical Laboratory Assessments

The safety laboratory test panels are shown in Table 11-1 and will be performed as indicated in Table 3-2. The timing of clinical laboratory assessments is described in Section 11.1. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate. Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology
Glucose	Hemoglobin
Blood urea nitrogen	Erythrocytes:
Creatinine	Mean corpuscular hemoglobin
Sodium	Mean corpuscular hemoglobin concentration
Potassium	Mean corpuscular volume
Calcium	Platelets
Chloride	Reticulocytes (absolute)
Magnesium	Leukocytes
Bicarbonate	Differential (absolute and percent):
Inorganic phosphate	Eosinophils
Total bilirubin, direct bilirubin	Basophils
Alkaline phosphatase	Neutrophils
Aspartate aminotransferase	Lymphocytes
Alanine aminotransferase	Monocytes
Lactate dehydrogenase	
Gamma glutamyl transferase	
Total protein	
Albumin	
Creatine kinase	
Amylase	
Lipase	

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

CF genotype (**Screening Period only**): Subjects without a documented genotype in their medical record will be tested to assess *CFTR* genotype.

For purposes of study conduct and data analysis, samples will be analyzed at a central laboratory. However, at the discretion of the local investigator, samples may be analyzed at a local laboratory for management of urgent medical issues, including if a subject cannot return to the clinical study site for the mandatory liver function testing (Section 11.5.3). If a local laboratory

test value is found to be abnormal and clinically significant, it will be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. If it is not possible to send a specimen to the central laboratory (e.g., the subject was hospitalized elsewhere) ideally within 48 to 72 hours, the investigator may base the assessment of an AE on the local laboratory value.

11.5.3 Elevation of Liver Function Test Parameters

Mandatory Liver Function Testing

Liver function testing ALT, AST, gamma-glutamyl transferase [GGT], alkaline phosphatase [ALP], and total bilirubin) must be performed while subjects are receiving study drug treatment (see Table 3-2 and Section 11.5.2). These blood samples should be processed and shipped immediately per the Laboratory Manual.

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

Study Drug Interruption

Study drug administration **must be interrupted** immediately, and the 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 LFTs (ALT, AST, and total bilirubin), study drug 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 study drug. Upon resumption of study drug, transaminases should be assessed weekly for 4 weeks. If a protocol-defined liver test elevation occurs within 4 weeks of rechallenge with study drug, then study drug 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, study drug 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.

11.5.4 Physical Examinations and Vital Signs

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

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

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 [e.g., oral or axillary]; however, the same method should be used at each visit]), pulse rate, and respiration rate. The subject should rest for at least 5 minutes before having vital signs measured; additional instructions will be included in a separate Study Reference Manual.

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

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

11.5.5 Ophthalmologic Examination

Ophthalmologic examinations will be performed by a licensed ophthalmologist or optometrist.

The OE includes

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

If a cataract is identified and determined to be clinically significant by the ophthalmologist or optometrist, the subject's caregiver and the Vertex medical monitor will be notified.

11.5.6 Contraception and Pregnancy

Not applicable.

12 STATISTICAL AND ANALYTICAL PLANS

This section presents a summary of the planned analyses for this protocol. Statistical analysis details for the interim analysis and the final analysis will be provided in the study statistical analysis plan (SAP), which will be finalized before the clinical data lock for the study and treatment unblinding. Details of analysis for the IDMC will be described in a separate IDMC SAP.

12.1 Sample Size and Power

There is limited information on the primary endpoint of MRI global chest score in this specific patient population. Only a small cohort of 17 patients similar to the patient population in this study, from Heidelberg, Germany, has some relevant information on this perspective. A vague normal prior distribution with a mean of 3.0 and an SD of 1000.0 for the mean change of MRI global chest score from baseline to the end of Year 1 in the placebo arm is used for the Bayesian sample size consideration.

The proposed sample size of 50 subjects (2:1 randomization: 33 LUM/IVA subjects and 17 placebo subjects after adjusting for a dropout rate of 10%) is also based on the number of potential subjects expected to be available for participation.

To illustrate potential outcomes, the Bayesian posterior probability that the mean change in the primary endpoint is better in the LUM/IVA group than placebo will be calculated.

For this study, a positive mean change of 3.0 points in the placebo arm (consistent with Heidelberg data) and a common SD of 5.0 in each arm were assumed. In this scenario, a maximum observed positive mean change of approximately 1.66 in the LUM/IVA arm would yield 80% Bayesian posterior probability of LUM/IVA being superior to placebo.

The actual Bayesian posterior probability of LUM/IVA being superior to placebo will be calculated using the actual observed mean change in the LUM/IVA arm and placebo arm at Week 48, which will serve as the primary analysis for this study. The primary endpoint and all secondary [redacted] endpoints specified in the protocol will also be analyzed using descriptive summary statistics. The reason for using descriptive summary statistics is due to the limited sample size and the associated insufficient power from the traditional statistical analysis perspective.

12.2 Analysis Sets

Assignment of subjects to analysis sets will be done before the clinical data lock for the study.

The **All Subjects Set** is defined as all subjects who have been randomized or have received at least 1 dose of study drug. This analysis set will be used in subject listings and a disposition summary table, unless otherwise specified.

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

The **Safety Set** is defined as all subjects who received at least 1 dose of study drug. The Safety Set will be used for all safety and tolerability analyses, in which subjects will be analyzed according to the treatment they received.

12.3 Statistical Analysis

The primary objective of this study is to explore the impact of LUM/IVA combination therapy on disease progression in subjects aged 2 through 5 years with CF, homozygous for *F508del*. The secondary objective is to explore the efficacy of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for *F508del*.

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

study. SAS® 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 for the study.

12.3.1 General Considerations

All individual subject data for all randomized subjects exposed to study drug will be presented in data listings.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, median, minimum value, and maximum value. The precision of the measurement for each continuous variable will be specified in the SAP.

Categorical variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place.

Baseline value, unless otherwise specified, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the initial administration of study drug. [redacted]

Change (absolute change) from baseline will be calculated as post-baseline value - baseline value. [redacted]

Relative change from baseline will be calculated as (post-baseline value - baseline value)/baseline value. [redacted]

The Treatment-emergent (TE) Period will include the time from the first dose to the Safety Follow-up Visit or 14 days after the last dose of the study drug for subjects who do not have a Safety Follow-up Visit. [redacted]

12.3.2 Background Characteristics

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

12.3.2.1 Subject Disposition

The number and percentage of subjects in the following categories will be summarized as appropriate:

- All Subjects Set
- Randomized
- Dosed (Safety Set)
- Randomized, dosed, and carry the intended *CFTR* mutation (FAS)

- Completed study drug treatment
- Prematurely discontinued the study during the Treatment Period and the reasons for discontinuation
- Completed study/Safety Follow-up Visit
- Prematurely discontinued the study and the reasons for discontinuation

12.3.2.2 Demographics, Medical History, and Baseline Characteristics

Demographics, medical history, and baseline characteristics will be summarized.

The following demographics and baseline characteristics will be summarized by initial dose group for the FAS: sex, race, ethnicity, age, weight, stature, region, baseline $LCI_{2.5}$, [redacted] baseline MRI global chest test score, [redacted]

12.3.2.3 Prior and Concomitant Medications

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

- **Prior medication:** any medication that started before initial dosing of study drug, regardless of when it ended
- **Concomitant medication:** medication continued or newly received at or after initial dosing of study drug through the end of the TE Period
- **Post-treatment medication:** medication continued or newly received beyond the TE Period

A given medication can be classified as a prior medication, a concomitant medication, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment. If a medication has a missing or partial missing start/end date or time and cannot be determined whether it was taken before initial dosing, concomitantly, or beyond the TE Period, it will be considered as prior, concomitant, and post-treatment.

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

12.3.2.4 Study Drug Exposure and Compliance

Exposure to study drug (i.e., duration of treatment) will be summarized for the FAS in terms of duration of treatment a subject received (in days), defined as the last day minus the first day of study drug plus 1.

Dosing compliance will be summarized for the FAS and is calculated as the actual number of dosing occasions at which study drug was taken (including when administered at study visits), as a percentage of the planned number of dosing occasions.

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

12.3.2.5 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Protocol deviations will be reviewed throughout the study. The rules for identifying an IPD will be described in the SAP.

All IPDs will be provided in an individual subject data listing, and summarized, as appropriate.

12.3.3 Efficacy Analysis

All efficacy analyses described in this section will be based on the FAS, unless specified otherwise. The analysis will include all available measurements through the last scheduled on-treatment visit, including measurements after treatment discontinuation.

12.3.3.1 Primary Analysis for the Study

The actual Bayesian posterior probability of LUM/IVA being superior to placebo will be calculated using the actual observed mean change in the LUM/IVA arm and placebo arm at Week 48, which will serve as the primary analysis for the study.

The primary endpoint and all secondary [redacted] specified in the protocol will also be analyzed using descriptive summary statistics. The reason for using descriptive summary statistics is due to the limited sample size and the associated insufficient power from the traditional statistical analysis's perspective.

12.3.3.2 Analysis of Primary Endpoint

The primary endpoint of absolute change in MRI global chest score from baseline at Week 48 will be analyzed using descriptive summary statistics for both between treatment arm difference and within-treatment change.

Descriptive summary statistics including number of subjects, mean, median, SD, minimum, and maximum, along with the corresponding 95% CIs from the descriptive summary statistics will be provided. Additional Bayesian summary statistics including the 95% credible intervals on the primary endpoint of absolute change in MRI global chest score from baseline at Week 48 might be explored and details will be provided in the SAP.

12.3.3.3 Analysis of Secondary Endpoints

- **Absolute change from baseline in $LCI_{2.5}$ through Week 48**

The secondary endpoint of absolute change in $LCI_{2.5}$ from baseline through Week 48 will be analyzed using descriptive summary statistics for both between treatment arm difference and within-treatment arm change. The change from baseline to the average of all post-baseline measures at scheduled visits will be used for this analysis. Additional summary of changes from baseline at each post-baseline time point (at Week 12, Week 24, Week 36, and Week 48) will be provided in a similar way.

Descriptive summary statistics including number of subjects, mean, median, SD, minimum, and maximum, along with the corresponding 95% CIs from the descriptive summary statistics will be provided.

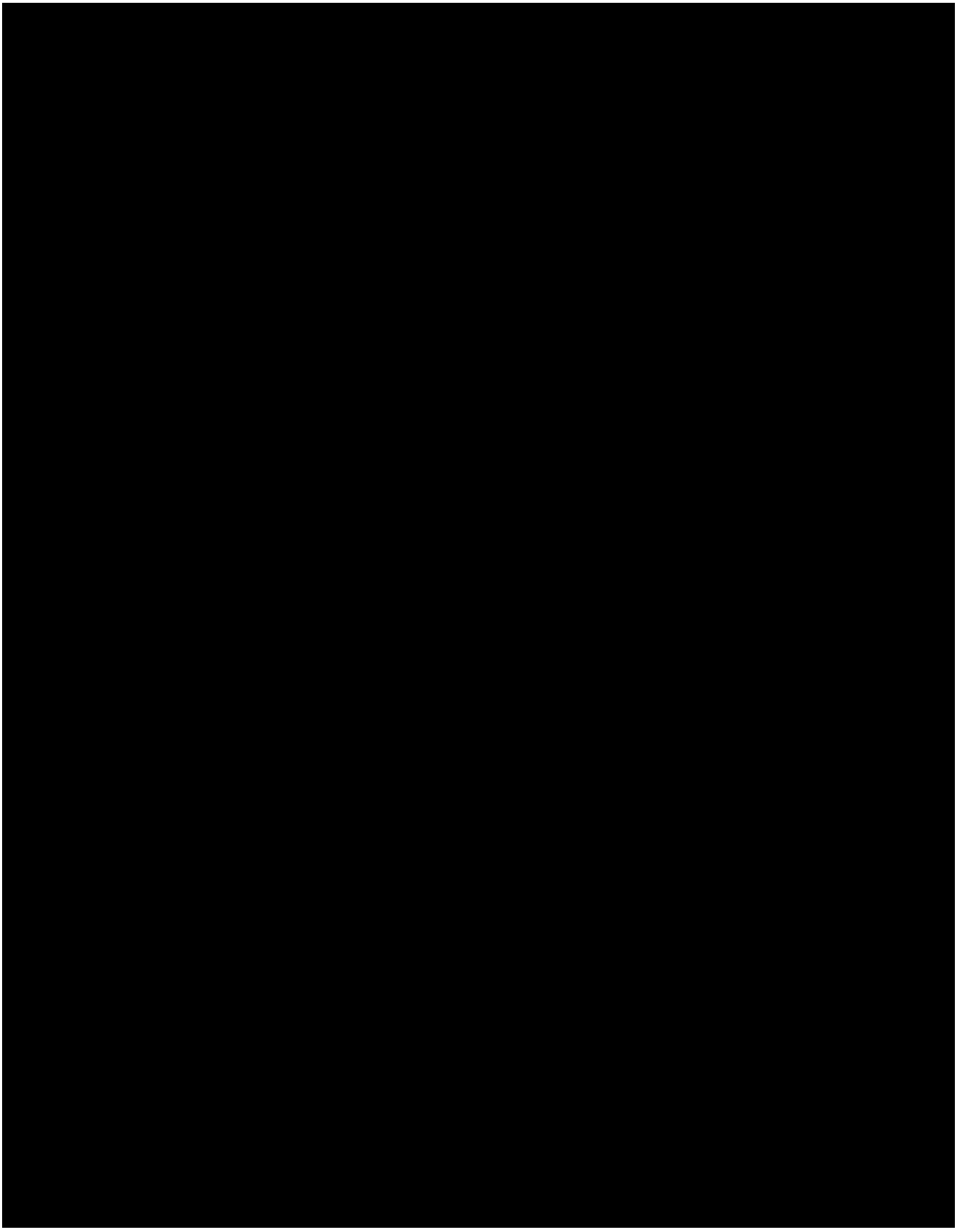
- **Absolute change from baseline in weight-for-age z-score at Week 48**

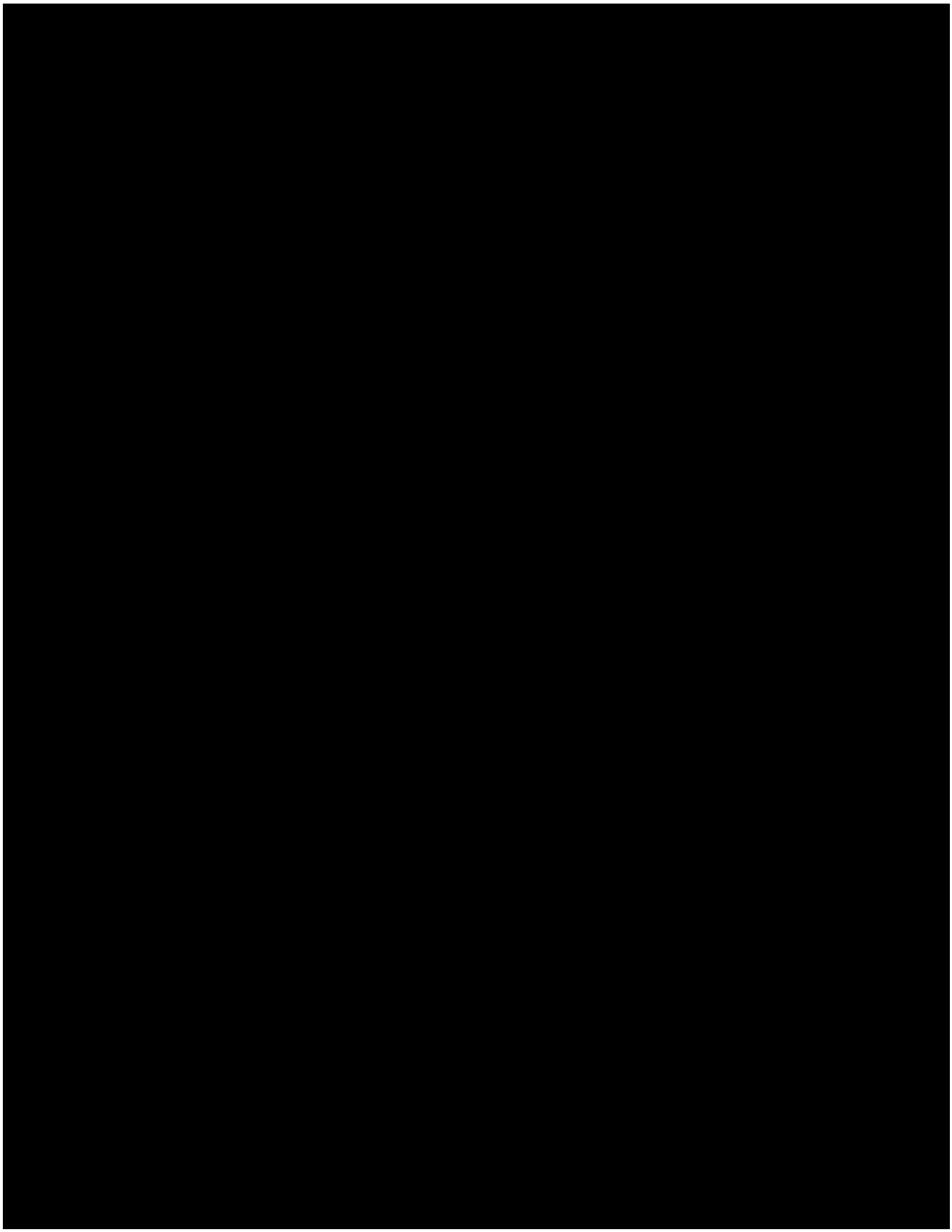
- **Absolute change from baseline in stature-for-age z-score at Week 48**
- **Absolute change from baseline in BMI-for-age z-score at Week 48**

For the absolute change from baseline at Week 48, the secondary endpoints above will be analyzed using descriptive summary statistics for both between treatment arm difference and within-treatment arm change. Additional summary of changes from baseline at each post-baseline time point (based on the actual time point of data collection for each of these secondary endpoints) will be provided in a similar way.

Descriptive summary statistics including number of subjects, mean, median, SD, minimum, and maximum, along with the corresponding 95% CIs from the descriptive summary statistics will be provided.

[redacted]





[redacted]

12.3.4 Safety Analysis

All safety analyses will be based on the set of data associated with the TE Period for subjects in the Safety Set.

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

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., hematology, serum chemistry)
- Vital signs
- OEs
- PEs

All safety data will also be presented in individual subject data listings. Safety endpoints will be analyzed based on the Safety Set. Only a descriptive analysis of safety will be performed.

12.3.4.1 Adverse Events

AEs will be classified as pretreatment AEs or TEAEs, defined as follows:

Pretreatment AE: any AE that started before the first dose date of study drug

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

For AEs with completely missing or partially missing 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 are described in the SAP.

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

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- TEAEs leading to death

Summaries will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT) using frequency counts and percentages (i.e., number and percentage of subjects with an 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 strongest relationship level will be presented in the relationship summaries.

In addition, a listing containing individual subject AE data for TEAEs leading to treatment discontinuation, SAEs, and deaths will be provided separately. All AEs, including pretreatment AEs, will be presented in an individual subject data listing.

12.3.4.2 Clinical Laboratory Assessments

For the treatment-emergent laboratory measurements, the raw values and change from baseline values of the continuous laboratory parameters will be summarized in SI units by treatment group at each scheduled time point. In addition, mean value at each visit will be plotted by treatment groups for each of the liver function parameters.

The number and percentage of subjects with at least 1 categorical change during the TE Period will be summarized by treatment group. The categorical (post-baseline) shift from baseline will also be summarized for selected laboratory parameters. The categorical criteria and the parameter selection criteria will be provided in the SAP. In addition, a listing containing individual subject laboratory assessment values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

12.3.4.3 Vital Signs

For the on-treatment vital signs measurements, the raw values and change from baseline values will be summarized by treatment group at each scheduled time point during the TE Period: systolic and diastolic blood pressure (mm Hg), pulse rate (beats per minute), and respiratory rate (breaths per minute).

Additional vital sign analyses will be described in the SAP, if applicable.

12.3.4.4 Ophthalmologic Examination

OE findings will be presented as a data listing only.

12.3.4.5 Physical Examination

PE findings will be presented as a data listing only.

12.3.4.6 Other Safety Analysis

The above safety analysis will be performed by treatment arm from baseline to Week 48, as well as from baseline to Week 96. In addition, a similar safety analysis like the above will be performed separately for placebo→LUM/IVA arm from Week 48 (before to LUM/IVA dose) through the end of the Safety Follow-up after Week 96, where predose measurement at Week 48 will be used as the baseline value.

Details of the analysis will be provided in the SAP.

12.3.5 Interim and IDMC Analyses

12.3.5.1 Interim Analysis

The primary analysis for Part 1 will be conducted after all subjects have completed Part 1 (i.e., up to and including the Week 48 Visit). The final analysis for Part 2 will occur after all

subjects have completed the study. Statistical analysis details for the interim analysis will be provided in the study SAP.

12.3.5.2 IDMC Analysis

An IDMC will be formed. The IDMC's objectives and operational details will be defined in a separate document (the IDMC charter). The IDMC will conduct regular planned safety reviews of study data as outlined in the IDMC charter.

Details of the IDMC analysis will be provided in a separate IDMC SAP.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

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

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

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

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

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

13.1.1.3 Documentation of Adverse Events

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

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, the earliest of
  - 18 days after the last dose of study drug, or
  - the ETT Visit, if that visit is 10 days or later following the last dose of study drug (see Section 9.1.4)

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

- Description of the event
- Classification of "serious" or "nonserious"
- Date of first occurrence and date of resolution (if applicable)
- Severity
- Causal relationship to study drug(s)
- Action taken
- Outcome
- Concomitant medication or other treatment given

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed August 2015). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." In considering the severity of an AE in a pediatric subject, the investigator will consider that reference ranges for pediatric clinical laboratory parameters may differ from those given in the CTCAE. The severity of an AE that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

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

13.1.1.5 Adverse Event Causality

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

Table 13-2 Classifications for AE Causality

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

13.1.1.6 Study Drug Action Taken

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

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

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

13.1.1.7 Adverse Event Outcome

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

Table 13-4 Classifications for Outcome of an AE

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

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

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

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

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the ICF was signed, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure will not be considered to indicate an

SAE, unless an AE caused the hospitalization or procedure to be rescheduled sooner or to be prolonged relative to what was planned. In addition, hospitalizations clearly not associated with an AE (e.g., social hospitalization for purposes of respite care) will not be considered to indicate an SAE.

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

13.1.2.2 Documentation of Serious Adverse Events

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

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

13.1.2.3 Reporting Serious Adverse Events

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

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

For questions, contact telephone: [redacted]

13.1.2.4 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities, 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/local IEC of all unexpected serious adverse drug reactions involving risk to human subjects.

13.2 Administrative Requirements

13.2.1 Ethical Considerations

The study will be conducted in accordance with the current ICH GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki (1996 Version), and in accordance with local applicable laws and regulations. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

13.2.2 Subject Information and Informed Consent

After the study has been fully explained, the subject’s legally appointed and authorized representative (e.g., parent or legal guardian) will sign and date an ICF and the subject will sign and date an assent form (if applicable) before study participation. The method of obtaining and documenting the informed consent and assent (if applicable) and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

13.2.3 Investigator Compliance

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

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

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

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 contact) of the last subject in the study.

13.3 Data Quality Assurance

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

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

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

13.4 Monitoring

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

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

13.5 Electronic Data Capture

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

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

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

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

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

13.6 Publications and Clinical Study Report

13.6.2 Clinical Study Report

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

14 REFERENCE

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[redacted]
32 Vertex Pharmaceuticals Incorporated. Lumacaftor/Ivacaftor Investigator's Brochure,
[redacted]

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX16-809-121	Version #: 4.0	Version Date: 24 July 2019
Study Title: An Exploratory Phase 2, 2-part, Randomized, Double-blind, Placebo-controlled Study With a Long-term, Open-label Period to Explore the Impact of Lumacaftor/Ivacaftor on Disease Progression in Subjects Aged 2 Through 5 years with Cystic Fibrosis, Homozygous for *F508del*		

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

[redacted]

15.2 Investigator Signature Page

Protocol #: VX16-809-121	Version #: 4.0	Version Date: 24 July 2019
Study Title: An Exploratory Phase 2, 2-part, Randomized, Double-blind, Placebo-controlled Study With a Long-term, Open-label Period to Explore the Impact of Lumacaftor/Ivacaftor on Disease Progression in Subjects Aged 2 Through 5 years with Cystic Fibrosis, Homozygous for *F508del*		

I have read Protocol VX16-809-121, Version 4.0, 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