1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

Vertex Study Number: VX15-809-110

[redacted]

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2 PROTOCOL SYNOPSIS

Title

A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

Clinical Phase and Clinical Study Type

Phase 3, safety and efficacy

Objectives

Primary Objective

To evaluate the long-term safety and tolerability of lumacaftor in combination with ivacaftor in subjects aged 6 years and older with cystic fibrosis (CF), homozygous for the *F508del-CFTR* mutation, who are in the Treatment Cohort

Secondary Objectives

- To evaluate the long-term efficacy and durability of lumacaftor in combination with ivacaftor for subjects in the Treatment Cohort
- To evaluate the post-treatment safety of lumacaftor in combination with ivacaftor for subjects in the Observational Cohort

Endpoints

Primary Endpoint

Treatment Cohort

Safety and tolerability assessments of long-term treatment of lumacaftor in combination with ivacaftor based on adverse events (AEs), clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis), standard 12-lead electrocardiograms (ECGs), vital signs, pulse oximetry, ophthalmological examinations, and spirometry

Observational Cohort

Not applicable

Secondary Endpoints

Treatment Cohort

The following efficacy endpoints will be analyzed using baseline values in the previous study (i.e., Study VX14-809-109 [Study 109], Study VX13-809-011B [Study 011B], or Study VX13-809-011B Lung Clearance Index [LCI] Substudy [Study 011B LCI Substudy]):

- Absolute change from baseline in $LCI_{2.5}$ (subjects from Study 109 and the Study 011B LCI Substudy only)
- Absolute change from baseline in sweat chloride
- Absolute change from baseline in body mass index (BMI)
- Absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score

The following efficacy endpoints will be analyzed using baseline values in the current study (Study VX15-809-110 [Study 110]):

- Absolute change from baseline in $LCI_{2.5}$ (subjects from Study 109 and the Study 011B LCI Substudy only)
- Absolute change from baseline in sweat chloride
- Absolute change from baseline in BMI

- Absolute change from baseline in CFQ-R respiratory domain score

Observational Cohort

Safety, as determined by serious adverse events (SAEs)

Other Secondary Endpoints

Treatment Cohort

The following efficacy endpoints will be analyzed using baseline values in the previous study (i.e., Study 109, Study 011B, or Study 011B LCI Substudy):

- Absolute change from baseline in LCI_{50} (subjects from Study 109 and the Study 011B LCI Substudy only)
- Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$)
- Relative change from baseline in $ppFEV_1$
- Absolute change from baseline in BMI-for-age z-score
- Absolute change from baseline in weight
- Absolute change from baseline in weight-for-age z-score
- Absolute change from baseline in height
- Absolute change from baseline in height-for-age z-score
- Absolute change from baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) domains
- Time-to-first pulmonary exacerbation, including pulmonary exacerbations in the previous study and the current study (subjects from Study 109 only)
- Event of having at least 1 pulmonary exacerbation, including pulmonary exacerbations in the previous study and the current study (subjects from Study 109 only)
- Number of pulmonary exacerbations, including pulmonary exacerbations in the previous study and the current study (subjects from Study 109 only)

The following efficacy endpoints will be analyzed using baseline values in the current study (Study 110):

- Absolute change from baseline in LCI_{50} (subjects from Study 109 and the Study 011B LCI Substudy only)
- Absolute change from baseline in $ppFEV_1$
- Relative change from baseline in $ppFEV_1$
- Absolute change from baseline in BMI-for-age z-score
- Absolute change from baseline in weight
- Absolute change from baseline in weight-for-age z-score
- Absolute change from baseline in height
- Absolute change from baseline in height-for-age z-score
- Absolute change from baseline in TSQM domains
- Time-to-first pulmonary exacerbation in the current study (subjects from Study 109 only)
- Event of having at least 1 pulmonary exacerbation in the current study (subjects from Study 109 only)
- Number of pulmonary exacerbations in the current study (subjects from Study 109 only)

The following efficacy endpoints will also be analyzed:

- Rate of change in LCI_{25} (subjects from Study 109 and the Study 011B LCI

Substudy only)

- Rate of change in $LCI_{5\,0}$ (subjects from Study 109 and the Study 011B LCI Substudy only)
- Rate of change in $ppFEV_1$

Observational Cohort

Not applicable

[redacted]

Number of Subjects

Approximately 256 subjects are potentially eligible to be enrolled into Study 110: approximately 200 subjects from Study 109 and approximately 56 subjects from Study 011B, if eligible.

Study Population

Male and female subjects aged 6 years and older with CF who are homozygous for the *F508del-CFTR* mutation and who participated in Study 109 or Study 011B

Investigational Drug

Active substance: lumacaftor and ivacaftor (fixed-dose combination with lumacaftor and ivacaftor)

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

Strength and Route of Administration: lumacaftor (LUM) 100-mg/ivacaftor (IVA) 125-mg tablets for oral administration in subjects aged 6 through 11 years and LUM 200-mg/IVA 125-mg tablets for oral administration in subjects aged 12 years and older

Dose investigated: LUM 200 mg every 12 hours (q12h)/IVA 250 mg q12h (2 × LUM 100-mg/IVA 125-mg tablet q12h) for subjects aged 6 through 11 years and LUM 400 mg q12h/IVA 250 mg q12h (2 × LUM 200-mg/IVA 125-mg tablet q12h) for subjects aged 12 years and older

Study Duration

Treatment Cohort

For the Treatment Cohort, study drug will be administered for approximately

96 weeks (or until commercial availability for eligible subject [redacted]) with a Safety Follow-up Visit 4 weeks [± 7 days] after the last dose).

Observational Cohort

For the Observational Cohort, maximum subject participation will be approximately 2 years.

Study Design

This is a Phase 3, multicenter study in subjects aged 6 years and older with CF who are homozygous for the *F508del-CFTR* mutation and who participated in Study 109 or Study 011B. Study 110 is designed to evaluate the safety and efficacy of long-term treatment of lumacaftor in combination with ivacaftor.

This study consists of a Treatment Cohort and an Observational Cohort. The Treatment Cohort and the Observational Cohort will be enrolled in parallel.

Treatment Cohort

The following subjects from Study 109 or Study 011B who meet the study criteria and elect to enroll in Study 110 are eligible for enrollment in the Treatment Cohort:

- Subjects who completed 24 weeks of study drug treatment (i.e., lumacaftor in combination with ivacaftor or placebo) in Study 109 or completed 24 weeks of study drug treatment and the Week 26 Safety Follow-up in Study 011B (NOTE: the last dose of study drug is the evening dose administered the day before the Week 24 Visit or the dose at the Week 24 Visit [based on the applicable protocol version for which a subject screens (provides consent/assent) under] in Study 109 or the evening dose administered the day before the Week 24 Visit in Study 011B)
- Subjects who are not receiving study drug treatment at the end of the Treatment Period in Study 109 or Study 011B (NOTE: subjects from Study 011B have a planned Washout Period from Week 24 to Week 26 and must still complete the Week 26 Safety Follow-up), including subjects who require study drug interruption to be either continued or initiated at Day 1 in Study 110, AND who have received Vertex approval for entry

Subjects who prematurely discontinued study drug treatment are not eligible for enrollment in the Treatment Cohort.

The Treatment Cohort will be open-label and will consist of the following dose regimens:

- LUM 200 mg q12h/IVA 250 mg q12h (subjects aged 6 through 11 years)
- LUM 400 mg q12h/IVA 250 mg q12h (subjects aged 12 years and older)

Subjects who turn 12 years of age in the previous study or Day 1 of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h on Day 1. Subjects who turn 12 years of age after the Day 1 Visit of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h at their next scheduled visit.

Observational Cohort

The following subjects from Study 109 or Study 011B who meet the study criteria and elect to enroll in Study 110 are eligible for enrollment in the Observational Cohort:

- Subjects who received at least 4 weeks of study drug in Study 109 or Study 011B and completed visits up to Week 24 of Study 109 or Week 26 of Study 011B but who are not eligible for the Treatment Cohort with lumacaftor in combination with ivacaftor
- Subjects who received at least 4 weeks of study drug in Study 109 or Study 011B (and did not prematurely discontinue study drug treatment) and completed visits up to Week 24 of Study 109 or Week 26 of Study 011B but who elect not to continue treatment with lumacaftor in combination with ivacaftor

Subjects in the Observational Cohort will not receive study drug and will have regularly scheduled telephone calls for approximately 2 years after their last dose of study drug in Study 109 or Study 011B to assess the post-treatment safety of lumacaftor and ivacaftor combination therapy.

Assessments

Efficacy Assessments

Subjects from Study 109 and the Study 011B LCI Substudy only: LCI (i.e., $LCI_{2.5}$ represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value and $LCI_{5.0}$ represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value)

Subjects from Study 109 only: Documentation of other events related to outcomes (e.g., pulmonary exacerbations), [redacted]

All subjects: Spirometry, sweat chloride, weight, height, BMI, CFQ-R, and TSQM

Safety Assessments

AEs, clinical laboratory assessments (serum chemistry, hematology, coagulation studies, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, ophthalmologic examinations, spirometry, and physical examinations (PEs)

[redacted]

Statistical Analyses

Statistical analysis details will be provided in the Statistical Analysis Plan (SAP). A stable draft SAP will be available before the first subject first dose in the

current open-label rollover study, which will be finalized before the clinical data lock for the study.

For the Treatment Cohort, analyses will be repeated for current dosing period, cumulative dosing period (efficacy only), and active dosing period. All analyses will be provided using all data, regardless of whether the subjects turn 12 years of age and subsequently switch to LUM 400 mg q12h/IVA 250 mg q12h [redacted]

For safety analysis, only descriptive analyses will be performed (i.e., no formal statistical testing will be performed). Summaries of treatment-emergent AEs (TEAEs) using number and percentages of subjects as well as number of events per 100 patient-years (number of events adjusted for the total duration of exposure) will be provided. Summaries of clinical laboratory results, ECGs, vital signs, and pulse oximetry, including their raw values and change from baseline values at each visit, will be provided. For the analysis of slit lamp lens, the number and percentage of subjects with shift changes from baseline (normal versus abnormal) will be tabulated. Ophthalmological examination findings will be presented as a listing. Spirometry data will also be summarized descriptively at each visit by category.

For continuous efficacy variables, raw values and absolute change (or relative change) from baseline at each visit will be summarized and plotted. Descriptive statistics including number of subjects (n), mean, standard deviation (SD), standard error (SE), median, minimum, and maximum will be provided. In addition, 95% CI of the mean will be presented. For the analyses of LCI and $ppFEV_1$, a mixed-effect repeated-measure model (MMRM) will be fitted for the cumulative dosing period, including visits from the previous Study 109 and Study 011B and visits from the current Study 110 based on Integrated Full Analysis Set (IFAS). In the MMRM models for the cumulative dosing period, the absolute change from baseline of the previous study (including all predose measurements at each visit in the cumulative dosing period, both on-treatment measurements and measurements after treatment discontinuation), will be included as the dependent variable; treatment group, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect with adjustment for previous study (Study 109 versus Study 011B), weight (<25 kg versus ≥25 kg), and $ppFEV_1$ severity (<90 versus ≥90), both as determined at screening in the previous study. In the analysis of LCI, baseline LCI value will also be included as a continuous covariate in the MMRM model. The result obtained from the model will be the treatment effect at each postbaseline visit. The estimated mean treatment effect, a 95% CI, and a 2-sided *P* value will be provided. The rate of change in LCI and $ppFEV_1$ during the active dosing period will be analyzed using linear mixed-effects models (LMM).

For the Observational Cohort, summaries will only be provided for the disposition, demographic and baseline characteristics, and SAEs, based on all enrolled subjects in that cohort.

IDMC Safety Reviews

An independent data monitoring committee (IDMC) will be formed using the [redacted]. The IDMC objectives and operational details will be defined in a separate document (IDMC Charter), which will be finalized before the first IDMC review meeting. The IDMC will conduct regular planned reviews of study data for the purpose of safety monitoring as outlined in the IDMC Charter.

3 SCHEDULE OF ASSESSMENTS

Schedules of Assessments are shown in Table 3-1 (Treatment Cohort) and Table 3-2 (Observational Cohort). All visits are to be scheduled relative to the Day 1 Visit (first dose of study drug). For example, the Week 8 (± 5 days) Visit would occur after 8 weeks of study drug administration has been completed (i.e., Day 57, first day of Week 9).

Table 3-1 Study VX15-809-110: Treatment Cohort

Event/Assessment[a]	Treatment Period								Early Treatment Termination Visit[c,d]	Safety Follow-up Visit (4 weeks [± 7 days] After Last Dose)[c,d]
	Day 1[b]	Day 3 (± 1 day)	Day 15 (± 3 days) and Week 4 (± 1 week)	Week 8, Week 16, Week 24, Week 36, Week 48 (± 1 week)	Week 12, Week 20 (± 1 week)	Week 60 Week 84 (± 1 week)	Week 72 (± 1 week)	Week 96 (± 1 week)		
Clinic visit	X		X	X	X[e,f]	X	X	X	X	X
Telephone contact[g]		X			X[f,h]					

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

[b] The Day 1 Visit of Study 110 will be on the **same day** as the Week 24 Visit (last Treatment Period visit) of Study 109 or the Week 26 Visit (Safety Follow-up Visit) of Study 011B for subjects at Study 110 sites that have been activated by the time the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B) has been completed. Subjects at these active sites will NOT have to repeat any Study 110 Day 1 assessments that were specified to be performed at the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B). Subjects at these active sites may return within 1 calendar day to complete the remaining Day 1 assessments (including administration of the Day 1 dose for subjects who receive the last Study 109 dose at the Week 24 Visit [see Section 10.2]) specific to Study 110. If study drug administration occurs when a subject returns the following calendar day, predose vital sign and spirometry assessments must be repeated before dosing. Subjects who were enrolled but had Day 1 study drug administration procedures (Section 10.2) delayed more than 1 calendar day will have to repeat all assessments (with the exception of the ophthalmologic examination if performed within the last 3 months before) that were specified to be performed at the Day 1 visit before receiving their first dose of study drug. The Day 1 Visit of Study 110 **will NOT coincide** with the Week 24 Visit (last Treatment Period visit) of Study 109 or the Week 26 Visit (Safety Follow-up Visit) of Study 011B for subjects at Study 110 sites that have NOT been activated by the time the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B) has been completed. Subjects at these nonactive sites will have to repeat any Study 110 Day 1 assessments (in addition to completing Study 110-specific Day 1 events/assessments) that were specified to be performed at the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B) except for the ophthalmologic examination (if the ophthalmologic examination was performed within the last 3 months before the visit).

[c] Subjects who prematurely discontinue study drug treatment during the Treatment Period in Study 110 will be asked to complete the Early Treatment Termination Visit and the Safety Follow-up Visit (Section 8.1.1.3). The Early Treatment Termination Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. If the Early Treatment Termination Visit occurs 3 weeks or later following the last dose of study drug, then the Safety Follow-up Visit will replace the Early Treatment Termination Visit (i.e., the assessments performed will be those specified for the Safety Follow-up Visit in Table 3-1), and an Early Treatment Termination Visit will not be required.

[d] With the exception of [redacted] subjects who cannot access the commercial product after regulatory approval because reimbursement by the subject's insurance carrier (whether government or private payer) is not yet available or because the subject lacks insurance coverage, subjects who become eligible to receive commercially-available LUM/IVA by prescription of a physician may be discontinued from study drug dosing and will complete the Early Treatment Termination Visit (before commercially-available LUM/IVA dosing begins). The Safety Follow-up Visit will not be required if the subject immediately continues on commercially-available LUM/IVA.

[e] LFTs (ALT, AST, GGT, ALP, and total bilirubin) will be performed at these visits. Although blood samples are to be collected and analyzed at a central laboratory, a local laboratory may be used if a subject cannot return to the clinical study site for the blood draw (Section 11.7.3).

[f] A urine pregnancy test will be performed for all female subjects of childbearing potential before the Week 12 and Week 20 telephone contacts, and the results made available before the contact. The urine pregnancy test may be performed at home or at the site.

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

[h] If a subject returns to the site for the Week 12 and/or Week 20 laboratory assessments, assessment of the subject's status, any AEs, concomitant medications, treatments, and procedures may be done in the clinic and telephone contact will not be required.

Table 3-1 Study VX15-809-110: Treatment Cohort

Event/Assessment[a]	Treatment Period								Early Treatment Termination Visit[c,d]	Safety Follow-up Visit (4 weeks [± 7 days] After Last Dose)[c,d]
	Day 1[b]	Day 3 (± 1 day)	Day 15 (± 3 days) and Week 4 (± 1 week)	Week 8, Week 16, Week 24, Week 36, Week 48 (± 1 week)	Week 12, Week 20 (± 1 week)	Week 60 Week 84 (± 1 week)	Week 72 (± 1 week)	Week 96 (± 1 week)		
Informed consent (and assent, if applicable)	X									
Inclusion/exclusion criteria review	X									
Urine β-hCG[i,j]	X		X	X	X[f]	X	X	X	X	X
CFQ-R[k]	X		X	Weeks 16, 24, 48				X	X[l]	X
TSQM[k]	X		X	Weeks 16, 24, 48				X	X[l]	X
Height and weight[m]	X		X	X		X	X	X	X	X
Vital signs[n]	X		X	X		X	X	X	X	X
Pulse oximetry[n]	X		X	X		X	X	X	X	X

i Pregnancy tests will be performed for all female subjects who are of childbearing potential from the time of the Day 1 Visit or at any point through the Safety Follow-up Visit (Section 11.7.8).

j See Section 11.7.2 for details.

k All questionnaires should be completed before the start of any other assessments. The CFQ-R (Section 11.6.5) should be completed first, followed by the TSQM (Section 11.6.6).

l Subjects will need to complete the questionnaires at the Early Treatment Termination Visit if it has been 2 weeks or more since they last completed the questionnaire.

m Height and weight will be measured before study drug dosing with shoes off (Section 11.6.4). BMI will be derived from this assessment.

n Vital signs and pulse oximetry will be collected before study drug dosing after the subject has been at rest (seated or supine) for at least 5 minutes (Section 11.7.4).

Table 3-1 Study VX15-809-110: Treatment Cohort

Event/Assessment[a]	Treatment Period								Early Treatment Termination Visit[c,d]	Safety Follow-up Visit (4 weeks [± 7 days] After Last Dose)[c,d]
	Day 1[b]	Day 3 (± 1 day)	Day 15 (± 3 days) and Week 4 (± 1 week)	Week 8, Week 16, Week 24, Week 36, Week 48 (± 1 week)	Week 12, Week 20 (± 1 week)	Week 60 Week 84 (± 1 week)	Week 72 (± 1 week)	Week 96 (± 1 week)		
Ophthalmologic examination[o]	X			Week 48[p]				X[p,q]	X[p,q]	X[p,q]
Full physical examination[r]	X							X	X	X
Standard 12-lead ECG[s]	X[t]		X	Weeks 8, 16, 24, 48			X	X	X	X
Serum β-hCG[i,j]	X									
Serum chemistry[j,u]	X		X	X	X[e,v] LFTs only	X[e,v] LFTs only	X	X	X	X
Hematology[j]	X		X	X			X	X	X	X
Coagulation studies[j]	X		X	Weeks 16, 24, 48				X		X
Urinalysis[j]	X			Weeks 16, 24, 48				X		X

[o] An ophthalmologic examination will be conducted by a licensed ophthalmologist or optometrist (Section 11.7.6). Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination. If a cataract or lens opacity is identified and determined to be clinically significant by a licensed ophthalmologist or optometrist at the Day 1 examination (also see Footnote b), the subject will be notified. After discussion with the site principal investigator and in collaboration with the Vertex medical monitor, the subject may elect to participate or not to participate in the study. If the subject continues in the study, more frequent ophthalmologic monitoring should be considered. If a cataract or lens opacity is identified and determined to be clinically significant by a licensed ophthalmologist or optometrist after dosing, the subject will be notified. After discussion with the site principal investigator, and in collaboration with the Vertex medical monitor, the subject may elect to continue or discontinue the study. If the subject discontinues study drug, they should complete the Early Treatment Termination Visit and Safety Follow-up Visit (see Section 8.1.1.3 for Early Treatment Termination). If the subject continues, more frequent ophthalmologic monitoring should be considered.

[p] Subjects may complete the ophthalmologic examination within ± 1 week of the scheduled visit.

[q] An ophthalmologic examination will be conducted by a licensed ophthalmologist or optometrist at the Week 96 Visit (or the Early Treatment Termination Visit if the subject does not have a Week 96 Visit) OR the Safety Follow-up Visit (Section 11.7.6). Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination.

[r] Symptom-directed physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator (Section 11.7.4).

[s] All standard 12-lead ECGs will be performed before study drug dosing and after the subject has been seated or supine for at least 5 minutes (Section 11.7.5). The ECG will be performed before any other procedures that may affect heart rate (e.g., blood draws).

[t] ECGs collected on Day 1 before study drug dosing will be performed in triplicate.

[u] LFTs (ALT, AST, GGT, ALP, and total bilirubin) must be performed at the scheduled visits and every 4 weeks (± 1 week) in between scheduled visits through Week 24 (Weeks 12 and 20) (Section 11.7.3). After this point, LFTs will be collected at subsequent scheduled clinic visits (Weeks 24, 36, 48, 60, 72, 84, and 96). Although blood samples are to be collected and analyzed at a central laboratory, a local laboratory may be used if a subject cannot return to the clinical study site for the blood draw.

[v] The liver function testing at Weeks 12, 20, 60, and 84 may be completed pre- or postdose.

Table 3-1 Study VX15-809-110: Treatment Cohort

Event/Assessment[a]	Treatment Period								Early Treatment Termination Visit[c,d]	Safety Follow-up Visit (4 weeks [± 7 days] After Last Dose)[c,d]
	Day 1[b]	Day 3 (± 1 day)	Day 15 (± 3 days) and Week 4 (± 1 week)	Week 8, Week 16, Week 24, Week 36, Week 48 (± 1 week)	Week 12, Week 20 (± 1 week)	Week 60 Week 84 (± 1 week)	Week 72 (± 1 week)	Week 96 (± 1 week)		
[redacted]										
Fecal elastase-1 (subjects from Study 109 only)[x]	X			Weeks 24, 48				X	X	
Sweat chloride[y]	X		X	Week 24				X	X	
Lung clearance index (subjects from Study 109 and the Study 011B LCI Substudy only)[z]	X		X	Weeks 24, 48				X	X	
Spirometry[aa]	X[bb]		X[bb]	X		X	X	X	X	X
Other events related to outcome (subjects from Study 109 only)[cc]	X		X	X		X	X	X	X	
[redacted]										

[x] Sweat collection will be done approximately at the same time as predose blood collections (Section 11.6.2).

[z] The LCI assessment will be performed pre-bronchodilator and before study drug dosing (Section 11.6.1). The assessment will be performed in triplicate and before the spirometry assessment.

[aa] Spirometry will be performed pre-bronchodilator for all spirometry assessments and before study drug dosing unless noted otherwise (Section 11.6.3).

[bb] On Days 1 and 15, spirometry will be performed before study drug dosing and at 2 hours (± 30 minutes) and 4 hours (± 30 minutes) postdose (Section 11.6.3).

[cc] Other events related to outcome include assessments relating to pulmonary exacerbations, administration of antibiotic therapy for sinopulmonary signs or symptoms, and hospitalizations (Section 11.6.7).

Table 3-1 Study VX15-809-110: Treatment Cohort

Event/Assessment[a]	Treatment Period								Early Treatment Termination Visit[c,d]	Safety Follow-up Visit (4 weeks [± 7 days] After Last Dose)[c,d]
	Day 1[b]	Day 3 (± 1 day)	Day 15 (± 3 days) and Week 4 (± 1 week)	Week 8, Week 16, Week 24, Week 36, Week 48 (± 1 week)	Week 12, Week 20 (± 1 week)	Week 60 Week 84 (± 1 week)	Week 72 (± 1 week)	Week 96 (± 1 week)		
[redacted]										
Meal(s) or snack(s) at site[ff]	X		X	X		X	X	X		
Study drug dosing[gg,ff]	**LUM 200 mg q12h/IVA 250 mg q12h OR LUM 400 mg q12h/IVA 250 mg q12h[hh]**									
Observation 4 hours after the first dose	X									
Study drug count			X	X		X	X	X		
Concomitant medications	**Continuous, from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit**									
Concomitant treatments and procedures	**Continuous, from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit**									
AEs and SAEs[ii]	**Continuous, from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit**									

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; β-hCG: beta-human chorionic gonadotropin; BMI: body mass index; CF: cystic fibrosis; CFQ-R: CF Questionnaire-Revised; [redacted]; ECG: electrocardiogram; GGT: gamma glutamyl transpeptidase; ICF: informed consent form; IEC: independent ethics committee; IRB: institutional review board; [redacted] IVA: ivacaftor; LCI: lung clearance index; LFT: liver function test; LUM: lumacaftor; [redacted] q12h: every 12 hours; SAE: serious adverse event; TSQM: Treatment Satisfaction Questionnaire for Medication.

[redacted]

Fat-containing food such as a standard CF high-fat, high-calorie meal or snack (Section 10.2) will be provided at the site to subjects after all predose assessments have occurred.

gg The study drug should be administered every 12 hours (± 2 hours) within 30 minutes of consuming fat-containing food (Section 10.2). On days of scheduled visits, the dose of study drug will be administered at the site after predose assessments have been completed. The last dose of study drug will be administered at the Week 96 Visit.

hh Subjects who turn 12 years of age in the previous study or Day 1 of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h on Day 1. Subjects who turn 12 years of age after the Day 1 Visit of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h at their next scheduled visit.

ii 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** as described in Section 13.1.2.2.

Table 3-2 Study VX15-809-110: Observational Cohort

Event/Assessment	Day 1[a]	Long-term Follow-up	
		Approximately Every 3 to 4 Months for the First Year	Approximately 2 Years (± 4 weeks)
Clinic visit	X		
Telephone contact		X	X
Informed consent/assent	X		
Inclusion criteria review	X		
Serious adverse events	**Continuous, from signing of ICF (and assent form, if applicable) through the last telephone contact**		

ICF: informed consent form.

[a] The Day 1 Visit of Study 110 will be on the **same day** as the Week 24 Visit (last Treatment Period visit) of Study 109 or the Week 26 Visit (Safety Follow-up Visit) of Study 011B for subjects at Study 110 sites that have been activated by the time the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B) has been completed. Subjects at these active sites will NOT have to repeat any Study 110 Day 1 assessments that were specified to be performed at the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B). The Day 1 Visit of Study 110 **will NOT coincide** with the Week 24 Visit (last Treatment Period visit) of Study 109 or the Week 26 Visit (Safety Follow-up Visit) of Study 011B for subjects at Study 110 sites that have NOT been activated by the time the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B) has been completed. Subjects at these nonactive sites will have to repeat any Study 110 Day 1 assessments (in addition to completing Study 110-specific Day 1 events/assessments) that were specified to be performed at the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B).

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMP	adenosine monophosphate
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	*CF transmembrane conductance regulator* gene
CFTR	CF transmembrane conductance regulator protein
CI	confidence interval
Cl^-	chloride ion
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ECG	electrocardiograms
eCRF	electronic case report form
EDC	electronic data capture
EENT	eyes/ears/nose/throat
EMA	European Medicines Agency
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
FEF	forced expiratory flow
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
G551D	*CFTR* missense gene mutation that results in the replacement of a glycine residue at position 551 of CFTR with an aspartic acid residue
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
GPS	Global Patient Safety
HBE	human bronchial epithelial
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
IA	interim analysis
ICF	informed consent form
ICH	International Conference on Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee

Abbreviation	Definition
IFAS	Integrated Full Analysis Set
IRB	institutional review board
[redacted]	[redacted]
IV	intravenous
IVA	ivacaftor
LCI	lung clearance index
LFT	liver function test
LMM	linear mixed-effects
LS	least squares
LUM	lumacaftor
[redacted]	[redacted]
MBW	multiple-breath washout
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures
[redacted]	[redacted]
n	number of subjects
P	probability
PCS	potentially clinical significant
PD	pharmacodynamic
PDCO	Pediatric Committee
PE	physical examination
[redacted]	[redacted]
PK	pharmacokinetic
$ppFEV_1$	percent predicted FEV_1
PR	PR interval
PT	preferred term
q12h	every 12 hours
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
ROS	Rollover Set
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SI	International System
SUSAR	suspected, unexpected, serious adverse reaction
TEAE	treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
[redacted]	[redacted]

5 INTRODUCTION

5.1 Background

Cystic fibrosis (CF) affects an estimated 70,000 children and adults worldwide[1] and is the most common fatal genetic disease in persons of European descent.[2] Based on the size of the population, CF qualifies as an orphan disease.[3,4] Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is in the mid-40s.[2,5] Although the disease affects multiple organs, most morbidity and mortality is caused by progressive loss of lung function.[6]

CF is an autosomal recessive genetic disease caused by a defect in the gene encoding the CF transmembrane conductance regulator (CFTR), an epithelial chloride ion (Cl^-) channel activated by cyclic AMP-dependent protein kinase A that is responsible for aiding in the regulation of salt and water absorption and secretion in various tissues.[2] This function is defective in patients with CF due to a loss of either cell surface expression and/or function.

More than 1900 mutations in the *CFTR* gene have been identified.[7] Mutations in the *CFTR* gene have been classified based on the molecular and functional consequence of the mutation on the CFTR protein[8,9,10] and can be generally considered to reduce the quantity of functional CFTR protein that reaches the epithelial cell surface or reduce the function of CFTR protein located at the cell surface. *CFTR* gene mutations that affect the quantity of functional cell surface CFTR protein include defects that reduce CFTR protein synthesis and defects that impede the cellular processing and delivery of CFTR proteins to the cell surface.

CFTR gene mutations associated with minimal CFTR function include

- mutations associated with severe defects in ability of the CFTR channel to open and close, known as defective channel gating or "gating mutations";
- severe defects in the cellular processing of CFTR and its delivery to the cell surface;
- no (or minimal) CFTR synthesis; and
- severe defects in channel conductance.

The most prevalent mutation is an in-frame deletion in the *CFTR* gene resulting in a loss of phenylalanine at position 508 in the CFTR protein (F508del-CFTR).[10] In the USA, almost 87% of patients with CF have at least 1 copy of the *F508del-CFTR* mutation, and approximately 47% have 2 copies.[11] In the European Union, approximately 83% of patients with CF have 1 or 2 copies of the *F508del-CFTR* mutation, and approximately 38.7% of patients with CF in the United Kingdom have 2 copies.[12] The *F508del-CFTR* mutation interferes with the ability of the CFTR protein to reach and remain at the cell surface, as well as to open and close, resulting in decreased Cl^- transport.[13,14] The combined effect is a marked reduction in F508del-CFTR-mediated Cl^- secretion that impairs fluid regulation and promotes accumulation of thick sticky mucus in the airway. The mucus build-up obstructs the airways and predisposes the patient to chronic lung infections.[15]

Two complementary approaches to increase CFTR-mediated Cl^- secretion in airway epithelia have been studied.[9] One approach is to treat with a compound that will modify the cellular processing and delivery of CFTR protein to the cell surface. This kind of compound has been termed a CFTR corrector. Another approach is to treat with a compound that increases channel gating activity of protein kinase A-activated CFTR at the cell surface to enhance ion transport. This kind of compound has been termed a potentiator. Depending on the amount of residual CFTR channel activity in the membrane and the pathophysiology of that activity (reflecting the CFTR genotype of the patient and possibly other factors), both approaches may be required to ameliorate lung disease in patients with CF. A modest restoration of Cl^- secretion through the action of a potentiator and/or corrector could prevent the hyperabsorption of water across the apical surface of epithelial cells, allowing for proper maintenance of airway hydration. Adequate airway hydration could alleviate the cycle of mucus plugging, infection, and inflammation that leads to irreversible structural changes in the lungs, and eventually respiratory failure for patients with CF.

Lumacaftor (also known as VX-809) is a compound developed by Vertex Pharmaceuticals Incorporated that has been shown to have CFTR corrector properties. Several lines of in vitro evidence suggest that lumacaftor works by promoting the proper folding of a fraction of F508del-CFTR protein during its biogenesis and processing in the endoplasmic reticulum, allowing it to exit the endoplasmic reticulum and traffic to the cell surface.[16,17] When added for more than 24 hours to human bronchial epithelial (HBE) cells isolated and cultured from lung explants obtained from donors with CF (CF-HBE cells) who are homozygous for the *F508del-CFTR* mutation, a concentration-dependent increase in levels of mature (i.e., plasma membrane) F508del-CFTR was observed. The increased trafficking of F508del-CFTR to the cell surface resulted in a significant increase in Cl^- secretion.[17] Lumacaftor did not correct the processing and localization of other misfolded or normally folded proteins other than CFTR, suggesting that the mechanism of lumacaftor action is selective for CFTR (CFTR corrector).[18,19]

Ivacaftor (also known as VX-770) is a compound developed by Vertex that has been shown to have CFTR potentiator properties. Proof of concept that pharmacologic modulation of CFTR function can result in clinical benefit in patients with CF was observed in subjects with CF and the *G551D* gating mutation who had robust clinical improvement following administration of ivacaftor.[20] Ivacaftor (150-mg tablets; Trade Name Kalydeco™) was approved in the United States, the European Union, and Canada in 2012 for the treatment of CF in patients 6 years of age and older who have a *G551D* mutation in the *CFTR* gene.

Lumacaftor in combination with ivacaftor is being developed for the treatment of CF in patients 6 years of age and older who are homozygous for the *F508del-CFTR* mutation. A summary of efficacy and safety data from studies evaluating lumacaftor in combination with ivacaftor is provided below.

Details about the lumacaftor/ivacaftor development program can be found in the Investigator's Brochure.[21]

5.2 Rationale for Present Study

Vertex has established efficacy, safety, and pharmacokinetics (PK) profiles for lumacaftor and ivacaftor combination therapy in subjects 12 years of age and older, who are

homozygous for the *F508del-CFTR* mutation (Studies VX12-809-103 [Study 103] and VX12-809-104 [Study 104]). In addition, preliminary safety and PK profiles for lumacaftor and ivacaftor combination therapy have been established in subjects 6 through 11 years of age, who are homozygous for the *F508del-CFTR* mutation (Study VX13-809-011 [Study 011] Part A). Ongoing Studies 011 Part B and VX14-809-109 [Study 109] are designed to obtain PK, safety, tolerability, pharmacodynamic (PD), and efficacy (Study 109 only) information to support an expanded indication for lumacaftor and ivacaftor combination therapy in the pediatric population (subjects 6 through 11 years of age, inclusive, who are homozygous for the *F508del-CFTR* mutation).

The long-term safety of lumacaftor in combination with ivacaftor has not yet been evaluated in subjects aged 6 through 11 years. Therefore, the primary objective of this study is to evaluate the long-term safety and tolerability of lumacaftor in combination with ivacaftor in subjects aged 6 years and older with CF, homozygous for the *F508del-CFTR* mutation.

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the long-term safety and tolerability of lumacaftor in combination with ivacaftor in subjects aged 6 years and older with CF, homozygous for the *F508del-CFTR* mutation, who are in the Treatment Cohort

6.2 Secondary Objectives

- To evaluate the long-term efficacy and durability of lumacaftor in combination with ivacaftor for subjects in the Treatment Cohort
- To evaluate the post-treatment safety of lumacaftor in combination with ivacaftor for subjects in the Observational Cohort

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Treatment Cohort

Safety and tolerability assessments of long-term treatment of lumacaftor in combination with ivacaftor based on adverse events (AEs), clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis), standard 12-lead electrocardiograms (ECGs), vital signs, pulse oximetry, ophthalmological examinations, and spirometry

Observational Cohort

Not applicable

7.2 Secondary Endpoints

Treatment Cohort

The following efficacy endpoints will be analyzed using baseline values in the previous study (i.e., Study VX14-809-109 [Study 109], Study VX13-809-011B [Study 011B], or Study VX13-809-011B Lung Clearance Index [LCI] Substudy [Study 011B LCI Substudy]):

- Absolute change from baseline in $LCI_{2.5}$ (subjects from Study 109 and the Study 011B LCI Substudy only)
- Absolute change from baseline in sweat chloride
- Absolute change from baseline in body mass index (BMI)
- Absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score

The following efficacy endpoints will be analyzed using baseline values in the current study (Study VX15-809-110 [Study 110]):

- Absolute change from baseline in $LCI_{2.5}$ (subjects from Study 109 and the Study 011B LCI Substudy only)
- Absolute change from baseline in sweat chloride
- Absolute change from baseline in BMI
- Absolute change from baseline in CFQ-R respiratory domain score

Observational Cohort

Safety, as determined by serious adverse events (SAEs)

7.3 Other Secondary Endpoints

Treatment Cohort

The following efficacy endpoints will be analyzed using baseline values in the previous study (i.e., Study 109, Study 011B, or Study 011B LCI Substudy):

- Absolute change from baseline in $LCI_{5.0}$ (subjects from Study 109 and the Study 011B LCI Substudy only)
- Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$)
- Relative change from baseline in $ppFEV_1$
- Absolute change from baseline in BMI-for-age z-score
- Absolute change from baseline in weight
- Absolute change from baseline in weight-for-age z-score
- Absolute change from baseline in height
- Absolute change from baseline in height-for-age z-score

- Absolute change from baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) domains
- Time-to-first pulmonary exacerbation, including pulmonary exacerbations in the previous study and the current study (subjects from Study 109 only)
- Event of having at least 1 pulmonary exacerbation, including pulmonary exacerbations in the previous study and the current study (subjects from Study 109 only)
- Number of pulmonary exacerbations, including pulmonary exacerbations in the previous study and the current study (subjects from Study 109 only)

The following efficacy endpoints will be analyzed using baseline values in the current study (Study 110):

- Absolute change from baseline in $LCI_{5.0}$ (subjects from Study 109 and the Study 011B LCI Substudy only)
- Absolute change from baseline in $ppFEV_1$
- Relative change from baseline in $ppFEV_1$
- Absolute change from baseline in BMI-for-age z-score
- Absolute change from baseline in weight
- Absolute change from baseline in weight-for-age z-score
- Absolute change from baseline in height
- Absolute change from baseline in height-for-age z-score
- Absolute change from baseline in TSQM domains
- Time-to-first pulmonary exacerbation in the current study (subjects from Study 109 only)
- Event of having at least 1 pulmonary exacerbation in the current study (subjects from Study 109 only)
- Number of pulmonary exacerbations in the current study (subjects from Study 109 only)

The following efficacy endpoints will also be analyzed:

- Rate of change in $LCI_{2.5}$ (subjects from Study 109 and the Study 011B LCI Substudy only)
- Rate of change in $LCI_{5.0}$ (subjects from Study 109 and the Study 011B LCI Substudy only)
- Rate of change in $ppFEV_1$

<u>Observational Cohort</u>

Not applicable

[redacted]

8 STUDY DESIGN

8.1 Overview of Study Design

This is a Phase 3, multicenter study in subjects aged 6 years and older with CF who are homozygous for the *F508del-CFTR* mutation and who participated in Study 109 or Study 011B. Study 110 is designed to evaluate the safety and efficacy of long-term treatment of lumacaftor in combination with ivacaftor.

This study consists of a Treatment Cohort and an Observational Cohort. The Treatment Cohort and the Observational Cohort will be enrolled in parallel as shown in Figure 8-1.

Treatment Cohort

The following subjects from Study 109 or Study 011B who meet the study criteria (Sections 9.1 and 9.2) and elect to enroll in Study 110 are eligible for enrollment in the Treatment Cohort:

- Subjects who completed 24 weeks of study drug treatment (i.e., lumacaftor in combination with ivacaftor or placebo) in Study 109 or completed 24 weeks of study drug treatment and the Week 26 Safety Follow-up in Study 011B (NOTE: the last dose of study drug is the evening dose administered the day before the Week 24 Visit or the dose at the Week 24 Visit [based on the applicable protocol version for which a subject screens (provides consent/assent) under] in Study 109 or the evening dose administered the day before the Week 24 Visit in Study 011B)

- Subjects who are not receiving study drug treatment at the end of the Treatment Period in Study 109 or Study 011B (NOTE: subjects from Study 011B have a planned Washout Period from Week 24 to Week 26 and must still complete the Week 26 Safety Follow-up), including subjects who require study drug interruption to be either continued or initiated at Day 1 in Study 110, AND who have received Vertex approval for entry

Subjects who prematurely discontinued study drug treatment are not eligible for enrollment in the Treatment Cohort.

The Treatment Cohort will be open-label and will consist of the following dose regimens:

- Lumacaftor (LUM) 200 mg every 12 hours (q12h)/ivacaftor (IVA) 250 mg q12h (subjects aged 6 through 11 years)
- LUM 400 mg q12h/IVA 250 mg q12h (subjects aged 12 years and older)

Subjects who turn 12 years of age in the previous study or Day 1 of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h on Day 1. Subjects who turn 12 years of age after the Day 1 Visit of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h at their next scheduled visit.

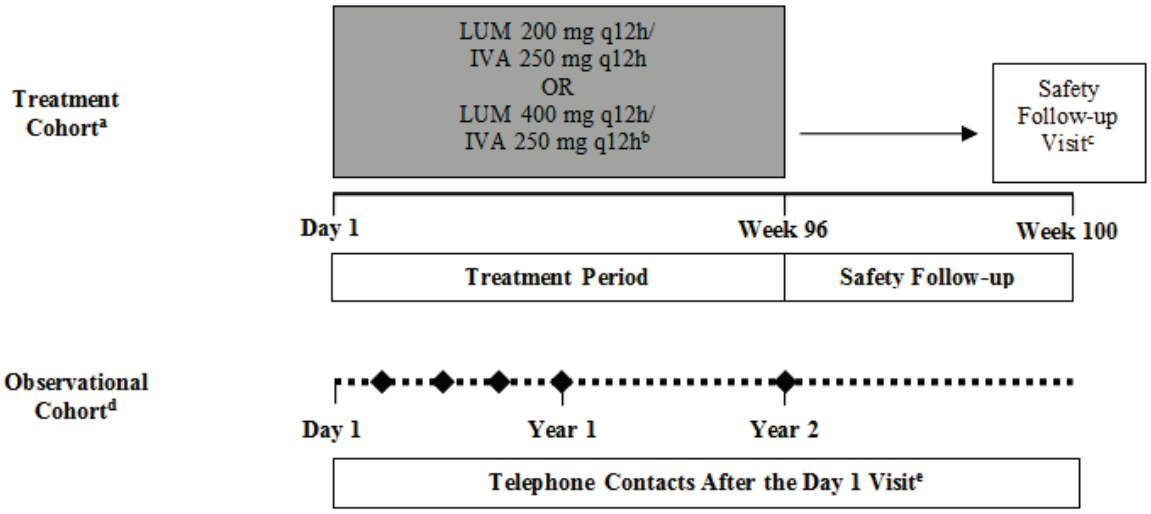
Observational Cohort

The following subjects from Study 109 or Study 011B who meet the study criteria (Section 9.1) and elect to enroll in Study 110 are eligible for enrollment in the Observational Cohort:

- Subjects who received at least 4 weeks of study drug in Study 109 or Study 011B and completed visits up to Week 24 of Study 109 or Week 26 of Study 011B but who are not eligible (Sections 9.1 and 9.2) for the Treatment Cohort with lumacaftor in combination with ivacaftor
- Subjects who received at least 4 weeks of study drug in Study 109 or Study 011B (and did not prematurely discontinue study drug treatment) and completed visits up to Week 24 of Study 109 or Week 26 of Study 011B but who elect not to continue treatment with lumacaftor in combination with ivacaftor

Subjects in the Observational Cohort will not receive study drug and will have regularly scheduled telephone calls for approximately 2 years after their last dose of study drug in Study 109 or Study 011B to assess the post-treatment safety of lumacaftor and ivacaftor combination therapy.

Figure 8-1 Schematic of Study Design



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

[a] The following subjects may be eligible for enrollment in the Treatment Cohort: (1) subjects who completed 24 weeks of study drug treatment (i.e., lumacaftor in combination with ivacaftor or placebo) in Study 109 or completed 24 weeks of study drug treatment and the Week 26 Safety Follow-up in Study 011B (NOTE: the last dose of study drug is the evening dose administered the day before the Week 24 Visit or the dose at the Week 24 Visit [based on the applicable protocol version for which a subject screens (provides consent/assent) under] in Study 109 or the evening dose administered the day before the Week 24 Visit in Study 011B) and (2) subjects who are not receiving study drug treatment at the end of the Treatment Period in Study 109 or Study 011B (NOTE: subjects from Study 011B have a planned Washout Period from Week 24 to Week 26 and must still complete the Week 26 Safety Follow-up), including subjects that require study drug interruption to be either continued or initiated at Day 1 in Study 110, AND who have received Vertex approval for entry. Subjects who prematurely discontinued study drug treatment are not eligible for enrollment in the Treatment Cohort.

[b] Subjects who turn 12 years of age in the previous study or Day 1 of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h on Day 1. Subjects who turn 12 years of age after the Day 1 Visit of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h at their next scheduled visit.

[c] The Safety Follow-up Visit is scheduled to occur 4 weeks (± 7 days) after the last dose of study drug.

[d] The following subjects from Study 109 or Study 011B may be eligible for enrollment in the Observational Cohort: (1) subjects who received at least 4 weeks of study drug in Study 109 or Study 011B and completed visits up to Week 24 of Study 109 or Week 26 of Study 011B but who are not eligible for the Treatment Cohort with lumacaftor in combination with ivacaftor and (2) subjects who received at least 4 weeks of study drug in Study 109 or Study 011B (and did not prematurely discontinue study drug treatment) and completed visits up to Week 24 of Study 109 or Week 26 of Study 011B but who elect not to continue treatment with lumacaftor in combination with ivacaftor

[e] A telephone contact will be made every 3 to 4 months during the first year and at approximately 2 years (± 4 weeks).

8.1.1 Treatment Cohort

8.1.1.1 Treatment Period

To participate in the study, the subject's parent or legal guardian must sign and date a study-specific informed consent form (ICF) and the subject must sign an assent form (if applicable) before any study-specific procedures can be performed. The ICF (and assent form, if applicable) will comply with all applicable regulations governing the protection of

human subjects and will be approved by Vertex and the site's institutional review board (IRB)/independent ethics committees (IEC).

After obtaining informed consent and assent (where applicable), subjects will receive the following treatment:

- LUM 200 mg q12h/IVA 250 mg q12h (subjects aged 6 through 11 years)
- LUM 400 mg q12h/IVA 250 mg q12h (subjects aged 12 years and older)

Subjects who turn 12 years of age in the previous study or Day 1 of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h on Day 1. Subjects who turn 12 years of age after the Day 1 Visit of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h at their next scheduled visit.

Dosing details are given in Section 10.

Timing of Day 1 Visit in Study 110 Active Sites

The Day 1 Visit of Study 110 will be on the **same day** as the Week 24 Visit (last Treatment Period visit) of Study 109 or the Week 26 Visit (Safety Follow-up Visit) of Study 011B for subjects at Study 110 sites that have been activated by the time the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B) has been completed. Subjects at these active sites will NOT have to repeat any Study 110 Day 1 assessments that were specified to be performed at the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B). Assessments for the Treatment Cohort are listed in Table 3-1. Subjects will be outpatients during the Treatment Period. All visits should occur within the windows specified.

Subjects at these active sites may return within 1 calendar day to complete the remaining Day 1 assessments (including administration of the Day 1 dose for subjects who receive the last Study 109 dose at the Week 24 Visit [see Section 10.2]) specific to Study 110. If study drug administration occurs when a subject returns the following calendar day, predose vital sign and spirometry assessments must be repeated before dosing.

Subjects who were enrolled but had Day 1 study drug administration procedures (Section 10.2) delayed more than 1 calendar day will have to repeat all assessments (with the exception of the ophthalmologic examination if performed within the last 3 months before) that were specified to be performed at the Day 1 visit before receiving their first dose of study drug.

Timing of Day 1 Visit in Study 110 Nonactive Sites

The Day 1 Visit of Study 110 **will NOT coincide** with the Week 24 Visit (last Treatment Period visit) of Study 109 or the Week 26 Visit (Safety Follow-up Visit) of Study 011B for subjects at Study 110 sites that have NOT been activated by the time the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B) has been completed. Subjects at these nonactive sites will have to repeat any Study 110 Day 1 assessments (in addition to completing Study 110-specific Day 1 events/assessments) that were specified to be performed at the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B) except for the ophthalmologic examination (if the ophthalmologic examination was performed within the last 3 months before the visit). Assessments for the Treatment Cohort for are listed in

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

8.1.1.2 Follow-up

The Safety Follow-up Visit is scheduled to occur 4 weeks (± 7 days) after the last dose of study drug for subjects in the Treatment Cohort. Safety Follow-up Visit assessments are listed in Table 3-1.

8.1.1.3 Early Treatment Termination

Subjects who prematurely discontinue study drug treatment during the Treatment Period in Study 110 will be asked to complete the Early Treatment Termination Visit and the Safety Follow-up Visit. The Early Treatment Termination Visit assessments are listed in Table 3-1.

The Early Treatment Termination Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. If the Early Treatment Termination Visit occurs 3 weeks or later following the last dose of study drug, then the Safety Follow-up Visit will replace the Early Treatment Termination Visit (i.e., the assessments performed will be those specified for the Safety Follow-up Visit in Table 3-1), and an Early Treatment Termination Visit will not be required.

With the exception of [redacted] subjects who cannot access the commercial product after regulatory approval because reimbursement by the subject's insurance carrier (whether government or private payer) is not yet available or because the subject lacks insurance coverage, subjects who become eligible to receive commercially-available LUM/IVA by prescription of a physician may be discontinued from study drug dosing and will complete the Early Treatment Termination Visit (before commercially-available LUM/IVA dosing begins). The Safety Follow-up Visit will not be required if the subject immediately continues on commercially-available LUM/IVA.

8.1.2 Observational Cohort

8.1.2.1 Day 1

To participate in the study, the subject's parent or legal guardian must sign and date a study-specific ICF and the subject must sign an assent form (if applicable) before any study-specific procedures can be performed. The ICF (and assent form, if applicable) will comply with all applicable regulations governing the protection of human subjects and will be approved by Vertex and the site's IRB/IEC.

Following consent and assent (where applicable), subjects will undergo the Day 1 assessments as shown in Table 3-2.

Timing of Day 1 Visit in Study 110 Active Sites

The Day 1 Visit of Study 110 will be on the **same day** as the Week 24 Visit (last Treatment Period visit) of Study 109 or the Week 26 Visit (Safety Follow-up Visit) of Study 011B for subjects at Study 110 sites that have been activated by the time the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B) has been completed. Subjects at these active sites will NOT have to repeat any Study 110 Day 1 assessments that were specified to be performed at the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B).

Timing of Day 1 Visit in Study 110 Nonactive Sites

The Day 1 Visit of Study 110 **will NOT coincide** with the Week 24 Visit (last Treatment Period visit) of Study 109 or the Week 26 Visit (Safety Follow-up Visit) of Study 011B for subjects at Study 110 sites that have NOT been activated by the time the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B) has been completed. Subjects at these nonactive sites will have to repeat any Study 110 Day 1 assessments (in addition to completing Study 110-specific Day 1 events/assessments) that were specified to be performed at the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B).

8.1.2.2 Long-term Follow-up

Subjects in the Observational Cohort will be followed for approximately 2 years. A telephone contact will be made every 3 to 4 months during the first year and at approximately 2 years (± 4 weeks) as shown in Table 3-2.

8.1.3 Lost to Follow-up

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

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

8.1.4 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will be formed using the [redacted] (Section 12.4.5.2). The IDMC objectives and operational details will be defined in a separate document (IDMC Charter) which will be finalized before the first IDMC review meeting. The IDMC will conduct regular planned reviews of study data for the purpose of safety monitoring as outlined in the IDMC Charter.

8.2 Rationale for Study Design and Study Drug Regimens

8.2.1 Study Design

This is a Phase 3, multicenter study in subjects aged 6 years and older with CF who are homozygous for the *F508del-CFTR* mutation and who participated in Study 109 or Study 011B.

The subjects studied are from the population that is expected to benefit from lumacaftor in combination with ivacaftor. This study is designed to evaluate the safety and efficacy of lumacaftor in combination with ivacaftor. This design is in harmony with guidelines for the study of human subjects, especially children, and balances safety concerns with potential benefits for the individual.

Because CF pulmonary disease progresses throughout life, it is not uncommon for patients in the 6- to 11-year age group to have well-preserved or even normal spirometry (e.g., $ppFEV_1$).[22,23,24,25] In spite of the potentially normal spirometry, patients in this age group with severe CF-causing mutations already have pulmonary structural aberrations

observed through computed tomography (CT) scans.[25,26,27,28,29,30] Consistent with these observations, impaired LCI, which measures the degree of small airway disease by assessing ventilation inhomogeneity, can be observed in pediatric patients with normal spirometry. These observations confirm that the disease process that results from a lack of CFTR activity begins early in life and before lung function as assessed by spirometry is affected. Because the underlying genetic and molecular etiology of the disease is consistent between this age group and older patients, it is anticipated that lumacaftor and ivacaftor combination therapy will be efficacious in this population as well.

Efficacy, safety, and PK profiles for lumacaftor and ivacaftor combination therapy have been established in subjects 12 years of age and older (Studies 103 and 104). In addition, preliminary safety and PK profiles for lumacaftor and ivacaftor combination therapy have been established in subjects 6 through 11 years of age (Study 011 Part A).

Ongoing Studies 011 Part B and 109 are designed to obtain PK, safety, tolerability, PD, and efficacy (Study 109 only) information to support an expanded indication for lumacaftor and ivacaftor combination therapy in the pediatric population (subjects 6 through 11 years of age, inclusive, who are homozygous for the *F508del-CFTR* mutation). Study 109 is designed to compare active treatment (LUM 200 mg q12h/IVA 250 mg q12h) with a matched placebo treatment for 24 weeks.

The long-term safety of lumacaftor in combination with ivacaftor has not yet been evaluated in subjects aged 6 through 11 years. Therefore, the primary objective of this study is to evaluate the long-term safety and tolerability of lumacaftor in combination with ivacaftor in subjects aged 6 years and older with CF, homozygous for the *F508del-CFTR* mutation, and who rollover from Study 109 or Study 011 Part B.

8.2.2 Study Drug Dose and Duration

Dose of Lumacaftor and Ivacaftor

Study 011 is a Phase 3, 2-part (Part A [completed] and Part B [ongoing]), open-label, multicenter study evaluating the PK, safety, tolerability, and PD (Part B only) of multiple doses of lumacaftor in combination with ivacaftor in subjects 6 through 11 years of age with CF who are homozygous for the *F508del-CFTR* mutation. Based on safety and PK results from Part A of Study 011, the dose regimen of LUM 200 mg q12h/IVA 250 mg q12h was chosen for continued development in subjects 6 through 11 years of age. In short, initial dose selection was conducted based on population PK model predictions. Subsequent analysis of the observed PK data from Part A of Study 011 confirmed that the exposures of lumacaftor at the LUM 200-mg q12h dose in subjects 6 through 11 years of age are consistent with exposures of lumacaftor at the LUM 400-mg q12h dose in subjects 12 years and older (VX09-809-102 [Study 102], Study 103, and Study 104). In addition, based on PK data from Part A of Study 011, the ivacaftor dose chosen in combination with lumacaftor in this study is expected to be within the clinical experience in subjects 12 years and older in the lumacaftor and ivacaftor combination program (Studies 102, 103, and 104) and the ivacaftor monotherapy program. Due to the induction effect of lumacaftor, the ivacaftor exposure in this study will not exceed previously observed exposures with ivacaftor monotherapy in the same age group.

Duration of Dosing

In Study 110, all subjects in the Treatment Cohort will receive lumacaftor in combination with ivacaftor. Subjects who received lumacaftor in combination with ivacaftor in the previous study as well as the current study may receive treatment for a total of approximately 2.5 years, providing further information on the safety and efficacy of long-term treatment with lumacaftor in combination with ivacaftor in subjects aged 6 years and older with CF who are homozygous for the *F508del-CFTR* mutation.

8.2.3 Rationale for Study Assessments

The safety assessments are standard parameters for clinical studies in drug development and are generally recognized as reliable, accurate, and relevant to the study of subjects with CF. Ophthalmologic examinations were added to the standard safety assessments.

Ophthalmologic Examinations: A juvenile rat toxicity study performed to support dosing of ivacaftor in subjects <2 years of age demonstrated lens opacities in some animals.[21] Prior studies in rats and dogs of older age did not demonstrate similar findings. Given substantial differences between human and rat lens development, the finding is of unlikely relevance to humans. Periodic ophthalmologic examinations for children aged 11 years and younger receiving ivacaftor are being performed to confirm this interpretation. The overall data acquired to date does not suggest an association between ivacaftor treatment and cataract development; however, a potential association has not been fully excluded.

LCI Assessment (Subjects From Study 109 and the Study 011B LCI Substudy Only): LCI is a measure of ventilation inhomogeneity that is based on tidal breathing techniques which have been evaluated in patients as young as infants.[31,32] Studies have shown that LCI correlates with FEV_1 in its ability to measure airway disease in patients with impacted spirometry assessment but can also detect lung disease at an earlier stage than spirometry.[28,33] Furthermore, data from Study VX10-770-106 in CF patients with an FEV_1 >90% showed LCI to be a more sensitive outcome measure than FEV_1.

Spirometry: Because lung disease is the major cause of morbidity and mortality for patients with CF, CF lung disease is the desired primary target of lumacaftor therapy. FEV_1, as measured by spirometry, is the most widely implemented standardized assessment to evaluate lung function in CF and is therefore included as an assessment.

Weight, Height, and BMI: Malnutrition is common in patients with CF because of increased energy expenditures due to lung disease and fat malabsorption. Given that lumacaftor in combination with ivacaftor is a systemic therapy, it has the potential to improve extrapulmonary manifestations of CF, including those in the gastrointestinal system. Improved nutritional status, defined as an increase in weight and/or BMI, is considered an appropriate endpoint for therapies targeting exocrine pancreatic manifestation of CF and was explored in previous clinical studies of CFTR-targeted therapies (Studies VX08-770-102 and VX08-770-103 and Studies 103 and 104).

As children gain weight and height as part of normal growth, adjustment for age and sex is necessary to assess changes in nutritional status in a population of boys and girls in varying stages of growth. To evaluate the effect of lumacaftor in combination with ivacaftor on growth and nutrition adjusted for age and sex, weight-for-age, height-for-age, BMI-for-age,

and the respective z-scores will be determined. Height and weight will be collected at the study visits indicated in the schedule of assessments.

Sweat Chloride: In patients with CF, the underlying CFTR ion transport defect results in elevated sweat electrolyte levels.[34,35] The sweat chloride test (quantitative pilocarpine iontophoresis) is the most common diagnostic tool for CF. A sweat chloride concentration of ≥60 mmol/L is considered to be diagnostic of CF, whereas <40 mmol/L is considered normal. Based on the mechanism of action of lumacaftor and ivacaftor, the sweat chloride test was included in this study as a measure of the PD effect on CFTR activity when lumacaftor is administered in combination with ivacaftor.

CFQ-R: The CFQ-R is a validated CF-specific instrument that measures the health-related quality of life of patients with CF.[36,37,38] The CFQ-R measures quality-of-life domains including respiratory symptoms, digestive symptoms, emotion, and health perception. Furthermore, the CFQ-R has been evaluated in clinical studies involving therapies for CF lung disease.[39,40,41] Linguistically-validated versions of the CFQ-R[42,43] are available, thereby allowing consistent interpretation of the results in global studies.

TSQM: TSQM is a widely used generic measure of satisfaction with medication. Its development involved a literature review about treatment satisfaction and qualitative research with patients with chronic illnesses.[44,45] It was originally validated in a sample of patients with a variety of chronic conditions but has been demonstrated to be a valid and reliable measure of satisfaction in patients with CF.[46] The domains of the TSQM measure effectiveness, side effects, convenience, and global satisfaction. Because treatment satisfaction is not measured with the other health-related quality-of-life measures in this study, the TSQM will be included as a study assessment for this purpose.

Other Events Related to Outcome (Subjects From Study 109 Only): These assessments (pulmonary exacerbations, administration of antibiotic therapy for sinopulmonary signs and symptoms, and hospitalizations) are other outcomes used to assess efficacy in therapies targeting improvement in CF disease. CF pulmonary exacerbations are a compilation of patient signs and symptoms that often result in the need for aggressive treatment, including the use of intravenous (IV) antibiotics that may require hospitalization. To date, there is no generally accepted objective definition of a pulmonary exacerbation,[47] and large multicenter CF clinical studies have used many variations of physician-derived definitions.[48,51] Despite the lack of a standard definition, reduction in pulmonary exacerbation rate has served as a key clinical efficacy measure in definitive CF clinical studies, supporting the registration of 2 chronic CF pulmonary therapies (inhaled recombinant human DNase and inhaled tobramycin).[47] To evaluate the potential effect of lumacaftor in combination with ivacaftor on pulmonary exacerbations, count, duration, and time-to-first event of hospitalizations and count and time-to-first event of IV courses of antibiotics for pulmonary exacerbations will be derived. For data consistency, this protocol specifies 1 definition of pulmonary exacerbation which is based on the definition used for the other studies including the ivacaftor monotherapy initial registration studies (Section 11.6.7.1). Because signs and symptoms in the definition may occur without meeting the overall definition of a pulmonary exacerbation, the number and timing of outpatient sick visits to the clinic or hospital for CF that are unrelated to the study protocol will also be collected.

9 STUDY POPULATION

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

9.1 Inclusion Criteria

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

1. Subject's legally appointed and authorized representative (e.g., parent or legal guardian) will sign and date an ICF and the subject will sign and date an assent form (if applicable).
2. Subjects entering the **Treatment Cohort** must meet both of the following criteria:
    - Completed 24 weeks of study drug treatment in Study 109 or completed 24 weeks of study drug treatment and the Week 26 Safety Follow-up in Study 011B (NOTE: the last dose of study drug is the evening dose administered the day before the Week 24 Visit or the dose at the Week 24 Visit [based on the applicable protocol version for which a subject screens (provides consent/assent) under] in Study 109 or the evening dose administered the day before the Week 24 Visit in Study 011B)
        - Subjects who had study drug interruptions, but completed study visits up to Week 24 of Study 109 or Week 26 of Study 011B are eligible (this is Day 1 of Study 110 for subjects at Study 110 active sites). Subjects who are not taking study drug at the end of the Treatment Period (NOTE: subjects from Study 011B have a planned Washout Period from Week 24 to Week 26 and must still

complete the Week 26 Safety Follow-up), including subjects who require study drug interruption to be either continued or initiated at Day 1 in Study 110, must have received Vertex approval for enrollment in the Treatment Cohort.

- Elect to enroll in the Treatment Cohort

NOTE: Subjects who prematurely discontinued study drug treatment are not eligible for enrollment in the Treatment Cohort.

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

- Completed 24 weeks of study drug treatment in Study 109 or completed 24 weeks of study drug treatment and the Week 26 Safety Follow-up in Study 011B (NOTE: the last dose of study drug is the evening dose administered the day before the Week 24 Visit or the dose at the Week 24 Visit [based on the applicable protocol version for which a subject screens (provides consent/assent) under] in Study 109 or the evening dose administered the day before the Week 24 Visit in Study 011B), but do not elect to enroll in the Treatment Cohort
- Subjects who received at least 4 weeks of study drug and completed visits up to Week 24 of Study 109 or Week 26 of Study 011B (this is Day 1 of Study 110 for subjects at Study 110 active sites) but are not taking study drug at the end of the Treatment Period (NOTE: subjects from Study 011B have a planned Washout Period from Week 24 to Week 26 and must still complete the Week 26 Safety Follow-up) because of a drug interruption and did not receive Vertex approval for enrollment into the Treatment Cohort (or elect not to enroll in the Treatment Cohort).
- Subjects who permanently discontinued study drug after receiving at least 4 weeks of study drug and remained in the study from the time of discontinuation of study drug treatment through the Week 24 Visit in Study 109 or the Week 26 Visit of Study 011B.

3. Subjects who are willing to remain on a stable CF medication regimen through the Safety Follow-up Visit (Treatment Cohort only).
4. As deemed by the investigator, the subject's legally appointed and authorized representative (e.g., parent or legal guardian) must be able to understand protocol requirements, restrictions, and instructions. The subject's legally appointed and authorized representative should be able to ensure that the subject will comply with, and is likely to complete, the study as planned.

9.2 Exclusion Criteria (Treatment Cohort Only)

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

1. History of any comorbidity or laboratory abnormality that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject (e.g., cirrhosis with portal hypertension).
2. Pregnant and nursing females. Females of childbearing potential must have a negative urine pregnancy test at the Day 1 Visit before receiving the first dose of study drug (Section 11.7.2).

3. Sexually active subjects of reproductive potential who are not willing to follow the contraception requirements outlined in Section 11.7.8.
4. History of drug intolerance in the prior study that would pose an additional risk to the subject in the opinion of investigator, and which should be discussed with the Vertex medical monitor. Examples of subjects who may not be eligible for the treatment cohort include (but are not limited to) the following:
    - Subjects with a history of allergy or hypersensitivity to the study drug
    - Liver function test (LFT) abnormality during study drug treatment in the previous study (Study 109 or Study 011B) for which a clear cause was not identified:
        - Abnormal liver function defined as any 2 or more of the following:
            a. ≥3 × upper limit of normal (ULN) aspartate aminotransferase (AST)
            b. ≥3 × ULN alanine aminotransferase (ALT)
            c. ≥3 × ULN gamma-glutamyl transpeptidase
            d. ≥3 × ULN alkaline phosphatase
        - ALT or AST >5 × ULN
        - Total bilirubin >2 × ULN
        - Other LFT abnormalities that would pose an additional risk to the subject in the opinion of investigator or Vertex
    - Other severe or life-threatening reactions to the study drug in the previous study
5. History of poor compliance with study drug and/or procedures in the previous study as deemed by the investigator.
6. Participation in an investigational drug trial (including studies investigating lumacaftor and/or ivacaftor). NOTE: participation in a noninterventional study (including observational studies, registry studies, and studies requiring blood collections without administration of study drug) is permitted.

9.3 Study Restrictions

For subjects enrolled in the Treatment Cohort, prohibited medications and certain foods are not allowed as 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

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

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

9.4 Prior and Concomitant Medications and Other Study Restrictions

9.4.1 Prohibited Medications

Prohibited medications as described in Table 9-1 are not allowed in this study while subjects are receiving study drug.

The use of cytochrome P450 (CYP) 3A substrates is not prohibited in this study, but investigators need to be aware that lumacaftor appears to be a strong inducer of this CYP isoenzyme. Therefore, the efficacy of drugs extensively metabolized by this isoenzyme may be affected. Each investigator should evaluate the benefit/risk ratio of using such drugs with lumacaftor during this study. Investigators should discuss any concerns regarding the use of CYP3A substrates during this study with the Vertex medical monitor or authorized designee.

The use of CYP2C and 2B6 substrates are not prohibited in this study, but investigators need to be aware that lumacaftor 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 ivacaftor may inhibit CYP2C9. Therefore, concomitant use of lumacaftor in combination with ivacaftor with CYP2B6, CYP2C8, CYP2C9, and CYP2C19 substrates may alter the exposure of these substrates.

Each investigator should evaluate the benefit-risk ratio of using such drugs with lumacaftor and ivacaftor during this study and discuss the use of these substrates during this study with the medical monitor or authorized designee.

The use of strong inhibitors of CYP3A is not prohibited in this study, but investigators need to be aware that a strong inhibitor of CYP3A has been shown to increase the exposure of ivacaftor when given in combination with lumacaftor; however, due to the induction effect of lumacaftor, the net exposure of ivacaftor is not expected to exceed previous experiences with ivacaftor monotherapy. Subjects who are using strong CYP3A inhibitors do not require study drug interruption. However, if they interrupt study drug for more than 72 hours, study drug resumption requires medical monitor discussion and approval. Each investigator should evaluate the benefit-risk ratio of using such drugs with lumacaftor and ivacaftor during this study and discuss the use of these strong inhibitors of CYP3A during this study with the medical monitor or authorized designee.

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

9.4.2 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 at, or after, completion of treatment in Study 109 or the Safety Follow-up Visit in Study 011B through the Safety Follow-up Visit of this study will be recorded in each subject's source documents and electronic case report form (eCRF).

- It is recommended that subjects continue to remain on a stable medication regimen for their CF from the previous study through the Safety Follow-up Visit in the current study. Stable medication regimen is defined as the current medication regimen for CF that subjects have been following for at least 4 weeks before Day 1.
- Information about bronchodilator use during the study will be collected and documented in the subject's source documents and eCRF. Subjects who are using a bronchodilator should have their spirometry assessments performed according to the guidelines provided in Section 11.6.3.

For subjects enrolled in the Observational Cohort, information regarding all prior and concomitant medications will not be collected.

9.5 Removal of Subjects From Study Drug Treatment

Subjects may discontinue study drug treatment at any time if the subject, investigator, or Vertex determines that it is not in the best interest of the subject to continue treatment.

The investigator should inquire about the reason for withdrawal, request that the subject return all unused study drug, and request that the subject return for an Early Treatment Termination Visit and Safety Follow-up Visit. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible.

A subject will be withdrawn from study drug treatment for the following reason:

- A female subject or a female partner of a male subject has a confirmed pregnancy

A subject may be withdrawn from study drug treatment after a discussion between the investigator and the medical monitor, for any of the following reasons:

- A subject develops a medical condition that requires prolonged concomitant therapy with a prohibited medication or prolonged interruption of the study drug.
- A subject develops a life-threatening AE or an SAE that places him/her at immediate risk, and discontinuation of study drug treatment and withdrawal from the study is deemed necessary.
- A subject is noncompliant with the study requirements.
- A subject has an increase in transaminases according to evaluations and management described in Section 11.7.3.
- A subject has an increase in QTc according to evaluations and management described in Section 11.7.5.

- With the exception of [redacted] subjects who cannot access the commercial product after regulatory approval because reimbursement by the subject's insurance carrier (whether government or private payer) is not yet available or because the subject lacks insurance coverage, subjects who become eligible to receive commercially-available LUM/IVA by prescription of a physician may be discontinued from study drug dosing and will complete the Early Treatment Termination Visit (before commercially-available LUM/IVA dosing begins). The Safety Follow-up Visit will not be required if the subject immediately continues on commercially-available LUM/IVA.

9.6 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 should continue to be followed, provided the subject has not withdrawn consent.

Subjects who discontinue study treatment early should return for the Early Treatment Termination Visit and the Safety Follow-up Visit, as noted in Section 8.1.1.3.

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 the Early Treatment Termination Visit, if applicable, and Safety Follow-up Visit, if applicable (see Section 8.1.1.3), and follow up with the subject regarding any unresolved AEs.

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

9.7 Replacement of Subjects

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

10 STUDY DRUG ADMINISTRATION 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 Administration

Study drug tablets will be administered orally as shown in Table 10-1. Subjects in the Observational Cohort will not receive study drug.

Table 10-1 Study Drug Administration

Treatment Cohort[a]	Time	LUM/IVA (100/125 mg per tablet)	LUM/IVA (200/125 mg per tablet)
LUM/IVA (LUM 200 mg q12h/IVA 250 mg q12h) for subjects aged 6 through 11 years	AM	2 tablets	none
	PM	2 tablets	none
LUM/IVA (LUM 400 mg q12h/IVA 250 mg q12h) for subjects aged 12 years and older	AM	none	2 tablets
	PM	none	2 tablets

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

[a] Subjects who turn 12 years of age in the previous study or Day 1 of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h on Day 1. Subjects who turn 12 years of age after the Day 1 Visit of the rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h at their next scheduled visit.

Study drug should be administered within 30 minutes of consuming fat-containing food such as a standard CF high-fat, high-calorie meal or snack according to the following guidelines:

1. All doses of study drug (morning and evening, as applicable) should be administered at approximately every 12 hours (± 2 hour) on each dosing occasion (e.g., if the morning doses of study drug are administered at 08:00 hours on Day 1, all subsequent morning doses should be administered between 06:00 hours and 10:00 hours).
2. For subjects at active sites who receive their last Study 109 dose at the Week 24 Visit, the Study 110 dose should be at least 6 hours after the Week 24 dose in Study 109; if the first Study 110 dose is not administered at the Study 109 Week 24/Study 110 Day 1 Visit, the first Study 110 dose will be the morning of the next calendar day.
3. All subjects will be observed for 4 hours after the first dose of the study drug.
4. On days of scheduled visits, with the exception of afternoon visits addressed below, the morning dose of study drug will be administered at the site after predose assessments have been completed. The meal or snack will be provided by the site for the morning dose of study drug.
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 of study drug and the morning dose will be administered in the clinic.
   - If the dose in the clinic will be more than 6 hours after the subject's scheduled morning dose, the subject should take the morning dose at home and the evening dose will be administered in the clinic. In this event, all assessments will be collected relative to the evening dose.
6. For visits after the Day 1 Visit, subjects will be instructed to bring all used and unused study drug to the site; study drug will be dispensed at each visit, as appropriate.
7. At the Week 96 Visit, the last dose of study drug will be administered.

10.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study. Randomization is not required because all subjects will be treated identically in the Treatment Cohort.

Subjects in the Observational Cohort will not receive study drug.

10.4 Study Drug Interruption

If study drug dosing must be interrupted for more than 72 hours, the medical monitor must be notified. In these instances, study drug dosing may only resume after approval by the medical monitor. Specific instructions for interruption for elevated LFT levels and elevated QTc levels are provided in Section 11.7.3 and Section 11.7.5.

10.5 Dose Modification for Toxicity

Modifications of the study drug dose are prohibited. If any unacceptable toxicity arises, study drug dosing will be discontinued for the individual subject (Section 8.1.1.3).

10.6 Packaging and Labeling

Vertex will supply the LUM 100-mg/IVA 125-mg tablets and LUM 200-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 lumacaftor and ivacaftor will be included in the Pharmacy Manual.

10.7 Study Drug Supply, Storage, and Handling

Table 10-2 provides the study drug information. The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for as detailed in Section 10.8. Detailed instructions regarding the storage, handling, and dispensation of the study drug will be provided in the Pharmacy Manual.

Table 10-2 Study Drug

Drug Name	Formulation/ Route	Packaging (Formulation Strength)	Storage Condition
Lumacaftor/ivacaftor (fixed-dose)	Fixed-dose tablet/ Oral	Supplied as 100-mg lumacaftor/125-mg ivacaftor tablets	Store at ≤25°C (77°F) with excursions to 30°C (86°F)
Lumacaftor/ivacaftor (fixed-dose)	Fixed-dose tablet/ Oral	Supplied as 200-mg lumacaftor/125-mg ivacaftor tablets	Store at ≤30°C (86°F)

10.8 Drug Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of (1) study drug received, (2) study drug dispensed to the subjects, and (3) study drug returned by the subjects. Subjects will be instructed to return all used and unused materials associated with the study drug to the site. These materials will be retained at

the site according to instructions provided by Vertex or its designee until inventoried by the study monitor. The study monitor will review study drug records and inventory throughout the study.

10.9 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subjects until the study monitor has performed drug accountability. The site monitor will instruct the site when it is appropriate to return or destroy study drug. If the site monitor authorizes destruction at the study site, the investigator, or designee, will ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Vertex. Destruction will be adequately documented. Procedures for destruction or return of the study drug will be detailed in the Pharmacy Manual.

10.10 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 of study drug dosing requirements. Compliance will also be assessed by ongoing study drug count.

If a subject 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. Subjects who prematurely discontinue study drug treatment during the Treatment Period in Study 110 will be asked to complete the Early Treatment Termination Visit and the Safety Follow-up Visit (Section 8.1.1.3).

10.11 Blinding and Unblinding

This will be an open-label study; however, subjects and their parent/caregiver should not be informed of their study-related LCI, spirometry, sweat chloride, [redacted] results during the study regardless if the subject has prematurely discontinued treatment or not.

11 ASSESSMENTS

11.1 Timing of Assessments

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

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

1. All questionnaires should be completed before the start of any other assessments scheduled at that visit. The CFQ-R should be completed first, followed by the TSQM.
2. Predose ECGs will be performed before any other procedures that may affect heart rate (e.g., blood draws).

3. The LCI assessment (performed for subjects from Study 109 and the Study 011B LCI Substudy only) should be performed before spirometry.

Additional timing notes

- The liver function testing at Weeks 12, 20, 60, and 84 may be completed pre- or postdose.
- The urine pregnancy tests at Weeks 12 and 20 may be completed pre- or postdose

[redacted]

11.2 Informed Consent/Assent

Subjects not of age of consent must assent, if applicable per local requirements, to participate in the study, and the subject's parent or legal guardian must sign and date a study-specific ICF before any study-specific procedures can be performed. The consent forms will comply with all applicable regulations governing the protection of human subjects. An ICF (and assent form, if applicable), approved by Vertex and the site's IRB/IEC, must be used.

11.3 Subject and Disease Characteristics

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

Age, sex, race, and ethnicity will be derived from the previous study because these data are required for the normalization of spirometry values using the Wang method (Section 11.6.3).

11.4 Pharmacokinetics

Not applicable

[redacted]

[redacted]

11.6 Efficacy

11.6.1 Lung Clearance Index

The LCI assessment will be conducted for subjects from Study 109 and the Study 011B LCI Substudy only.

The LCI assessments, derived from N_2-multiple-breath washout (MBW) testing, will be conducted at visits specified in Table 3-1 to evaluate the effect of lumacaftor in combination with ivacaftor on LCI and for evaluation of correlations between LCI and sweat chloride, and correlations between LCI and spirometry parameters. $LCI_{2.5}$ represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value whereas $LCI_{5.0}$ represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value. [61]

Each MBW will be performed in triplicate for each visit and the final LCI value will be calculated from the technically acceptable washout replicates by a central reader. The final LCI value at each visit will be the value provided by the LCI vendor based on the triplicates. The time for performing this test (in triplicate) during the study is approximately 1 hour at each study visit.

Pre-bronchodilator MBW testing is defined as MBW testing performed for subjects who have

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

All MBW testing should be performed "pre-bronchodilator." During the Treatment Period, MBW testing must be performed before dosing, unless noted otherwise. In the event that a subject forgets to withhold bronchodilator(s), MBW testing should be performed according to the following:

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

The MBW testing should be performed before the spirometry assessment (Section 11.6.3). Subjects and parents/caregivers should not be informed of study-related LCI results.

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

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

11.6.2 Sweat Chloride

The sweat chloride test is a standard diagnostic tool for CF, serving as a biomarker of CFTR activity. Collection of sweat samples will be performed at visits specified in Table 3-1 using an approved collection device. Sweat samples will be sent to a central laboratory for testing and interpretation of results. Individual sweat chloride test results will not be disclosed to the study sites. Specific instructions for collection, handling, processing, and shipping of sweat chloride samples to the central laboratory will be provided separately. The sweat chloride test must be conducted predose relative to the morning dose of study drug during the Treatment Period. At each time point, 2 samples will be collected, 1 sample from each arm (left and right).

Subjects and their parent/caregiver should not be informed of their study-related sweat chloride results during the study regardless if the subject permanently discontinues treatment or not.

11.6.3 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines[62] at the time points noted in Table 3-1 according to the additional guidelines that follow.

Pre-bronchodilator spirometry is defined as spirometry testing performed for subjects who have

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

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

All spirometry assessments should be performed "pre-bronchodilator." During the Treatment Period, spirometry assessments must be performed before dosing, unless noted otherwise. In the event that a subject forgets to withhold bronchodilator(s), spirometry should be performed according to the following:

- If a subject's Day 1 spirometry from Study 109 or Study 011B is pre-bronchodilator, but on a subsequent visit, the subject forgets to withhold bronchodilator use, a post-bronchodilator spirometry will be obtained for that visit only, and the visit will not be rescheduled.
- If, on Day 1 of Study 109 or Study 011B, the subject forgets to withhold his/her dose of bronchodilator, spirometry should be performed post-bronchodilator and all subsequent spirometric measurements in Study 110 (according to the schedule of assessments detailed in Table 3-1) should be performed post-bronchodilator.
- Each spirometry assessment will be recorded in the source documents as pre-bronchodilator or post-bronchodilator.

The parameters listed below will be normalized using the standards of Wang et al.[63]

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

All sites will be provided with spirometers and associated materials to be used for all study assessment by the central spirometry service. Spirometry data will be transmitted to a centralized spirometry service for quality review.

Subjects and their parent/caregiver should not be informed of their study-related spirometry results during the study regardless if the subject permanently discontinues treatment or not.

11.6.4 Weight, Height, and BMI

Weight and height will be assessed and BMI will be derived. Weight and height will be measured with shoes off at time points noted in Table 3-1. Weight and height will be measured before the dose of the study drug during the Treatment Period.

11.6.5 Cystic Fibrosis Questionnaire-Revised

The questionnaires provide information about demographics; general quality of life, school, work, or daily activities; and symptom difficulties (pertaining to CF). Copies of the CFQ-R used in this study will be provided in the Study Reference Manual. Validated translations[42,43] of the CFQ-R, if available, will be provided for participating centers in non-English-speaking

countries (if applicable). The CFQ-R should be completed before the start of any assessments scheduled at that visit.

Subjects will be asked to complete the CFQ-R in their native language, if validated translations are available.[36,38] The CFQ-R will be completed before dosing at visits noted in Table 3-1. At the Day 1 Visit of Study 110, subjects will complete the same version of the CFQ-R that was completed in the previous study (Study 109 or Study 011B). Subjects who are ≥12 years of age after the Day 1 Visit will complete the CFQ-R Child Version themselves, and their parents/caregivers will complete the CFQ-R Parent Version, on all visits, regardless of whether the subject subsequently turns 14 years of age during the study.

11.6.6 Treatment Satisfaction Questionnaire for Medication

Subjects will complete the TSQM before dosing at visits noted in Table 3-1. The TSQM is a widely used generic measure of satisfaction with medication. The domains of the TSQM measure effectiveness, side effects, convenience, and global satisfaction. Because treatment satisfaction is not measured with the other health-related quality-of-life measures in this study, the TSQM will be included as a study assessment for this purpose. Translations of the TSQM will be provided for participating centers in non-English-speaking countries (if applicable). The TSQM must be completed after the CFQ-R and before the start of any other assessments scheduled at that visit.

Subjects should be instructed to complete the TSQM questionnaire on Day 1 based on their experience of their current medication regimen over the prior 2 to 3 weeks. For all subsequent visits, subjects should be instructed to complete the TSQM based on their experience of the study drug over the prior 2 to 3 weeks. Subjects who discontinue study drug permanently, or who have interrupted study drug, will still complete the TSQM based on their experience of the study drug if taken during the prior 2 to 3 weeks. If study drug was not taken during this period, the responses should be based on their experience of their current medication regimen.

11.6.7 Other Events Related to Outcome

Other events related to outcome will be assessed for subjects from Study 109 only.

11.6.7.1 Antibiotic Therapy for Sinopulmonary Sign/Symptoms

New or changed antibiotic therapy (IV, inhaled, or oral) for the following sinopulmonary signs/symptoms will be determined and documented at visits as indicated in Table 3-1:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature above 38°C (equivalent to approximately 100.4°F)
- Anorexia or weight loss

- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination (PE) of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

For this study, pulmonary exacerbation is defined as a new, or change in, antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the above signs/symptoms. This definition is based on the definition of a pulmonary exacerbation used in previous clinical studies, including ivacaftor clinical studies.[48,64]

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

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

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

11.6.7.2 Hospitalization for CF

At visits indicated in Table 3-1, subjects will be queried about planned and unplanned hospitalizations lasting ≥24 hours. The dates for hospitalizations and the reasons for hospitalizations will be documented.

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

The following information will be determined:

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

11.7 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, pulse oximetry, ECGs, PEs, ophthalmologic examinations, and spirometry.

11.7.1 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 eCRF completion guidelines for investigators as well as training will be provided.

11.7.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory with the exception of urine pregnancy tests, which will be analyzed locally. Although blood samples are to be collected and analyzed at a central laboratory, a local laboratory may be used if a subject cannot return to the clinical study site for the mandatory liver function testing (Section 11.7.3).

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

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

Table 11-1 Safety Laboratory Test Panels

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

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

Pregnancy testing for female subjects who are of childbearing potential from the time of the Day 1 Visit or at any point through the Safety Follow-up Visit (as defined in Section 11.7.8.1):

Serum samples will be obtained as specified in Table 3-1 and analyzed at the central laboratory. Urine beta-human chorionic gonadotropin tests will be performed at the site as specified in Table 3-1. The urine pregnancy test on Day 1 must be negative before the first dose of study drug. The urine pregnancy tests at Weeks 12 and 20 may be performed at home or at the site.

If a urine pregnancy test is positive, all study drug dosing will stop and the pregnancy will be confirmed with a serum beta-human chorionic gonadotropin test. If confirmed, the pregnancy will be reported and the subject will be permanently withdrawn from study drug dosing as discussed in Section 11.7.8.2. If a pregnancy test is positive, the procedures outlined in Section 11.7.8.2 will be followed.

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

For purposes of study conduct, only laboratory tests done in the central laboratory may be used. Local laboratories may be used at the discretion of the local investigator for management of urgent medical issues. If a local laboratory test value is found to be abnormal

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

11.7.3 Elevation of Liver Function Test Parameters

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

Study Drug Interruption

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.

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

Resumption of Study Drug

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

Mandatory Liver Function Testing

Liver function testing (ALT, AST, gamma glutamyl transpeptidase, alkaline phosphatase, and total bilirubin) must be performed while subjects are receiving study drug treatment (Day 1, Day 15, and at a minimum of every 4 weeks after Week 4 as noted in Table 3-1). These blood samples should be processed and shipped immediately per the Laboratory Manual.

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

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

11.7.4 Physical Examinations, Vital Signs, and Pulse Oximetry

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

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

Vital signs include blood pressure (systolic and diastolic), temperature, pulse rate, and respiration rate. These will be assessed following a 5-minute rest in the seated or supine position.

Arterial oxygen saturation by pulse oximetry is a noninvasive measure of oxygen delivery to the tissues and has been correlated with clinical status and lung function. These will be assessed following at least a 5-minute rest in the seated or supine position.

11.7.5 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout according to the Schedule of Assessments (Table 3-1). Standard 12-lead ECGs will be performed with central over-reading. All sites will be provided with ECG machine(s) and associated materials by the central ECG diagnostic service.

Additional standard 12-lead ECGs will be performed at any other time if clinically indicated.

The performance of all ECGs will adhere to the following guidelines:

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

The ECG traces will be manually read at the study site at the Day 1 and Safety Follow-up Visits. A printout of the ECG traces will be made for safety review by the investigator and maintained with source documentation. Clinically significant ECG abnormalities occurring during the study through the Safety Follow-up Visit will be recorded as AEs.

A hard copy of the ECG will be printed and signed by the investigator at the site. To ensure the safety of the subjects, the investigator or designee at the investigator site will make comparisons to the predose measurement at Day 1 (baseline [Study 109 for subjects from Study 109 and Study 110 for subjects from Study 011B]). If the QTcF is increased by >45 msec from the shortest baseline QTcF or the absolute QTcF value is ≥500 msec for any scheduled ECG, 2 additional ECGs will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>45 msec from baseline or ≥500 msec), a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

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

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

If the QTc value remains above the threshold value (>45 msec from baseline or ≥500 msec) on repeated measurement, or is noted on 2 or more occasions with no identified alternative etiology for the increased QTc study drug, then discontinuation from study drug treatment may be required after discussion with the Vertex medical monitor or designee.

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

11.7.6 Ophthalmologic Examination

Subjects will undergo an ophthalmologic examination at the Day 1 and Week 48 Visit and at the Week 96 Visit (or the Early Treatment Termination Visit if the subject does not have a Week 96 Visit) OR the Safety Follow-up Visit (NOTE: subjects may complete the ophthalmologic examination within ± 1 week of the scheduled Week 48, Week 96/Early Treatment Termination, and Safety Follow-up Visits), which includes

- measurement of best corrected distance visual acuity of each eye
- measurement of lens refracting power (e.g., autorefractor or ophthalmoscopy streak following cycloplegia)
- pharmacologically dilated examination of the lens with a slit lamp

These examinations must be conducted by a licensed ophthalmologist or optometrist. Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination.

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

If a cataract or lens opacity is identified and determined to be clinically significant by a licensed ophthalmologist or optometrist after dosing, the subject will be notified. After discussion with the site principal investigator and in collaboration with the Vertex medical monitor, the subject may elect to continue or discontinue the study. If the subject discontinues study drug, they should complete the Early Treatment Termination Visit and Safety Follow-up Visit (see Section 8.1.1.3 for Early Treatment Termination). If the subject continues, more frequent ophthalmologic monitoring should be considered.

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

11.7.7 Spirometry

Refer to Section 11.6.3 for the spirometry assessment.

11.7.8 Contraception and Pregnancy

Standard contraception- and pregnancy-related information and requirements are provided below. It should be noted that some of this information and requirements may have limited applicability in this pediatric population.

11.7.8.1 Contraception

The effects of lumacaftor and ivacaftor combination therapy on conception, pregnancy, and lactation in humans are not known. Neither lumacaftor nor ivacaftor showed any genotoxic potential in a standard battery of in vitro (Ames, Chinese hamster ovary cell chromosomal aberration) and in vivo (mouse micronucleus) studies. Lumacaftor and ivacaftor were each found to be non-teratogenic in reproductive toxicology studies in rats and rabbits (see the lumacaftor/ivacaftor Investigator's Brochure[21]). However, a metabolite of lumacaftor, M28-lumacaftor, when given to pregnant rats at very high levels far beyond levels observed in humans (>100-fold), produced fetal malformations. The significance of this finding in humans is unclear, but is highly unlikely to be of any clinical significance. Subjects should follow the contraception requirements outlined in this study protocol. The effects of lumacaftor in combination with ivacaftor on the PK of hormonal contraceptives are not known; however, since lumacaftor is an inducer of CYP3A, it may reduce the effectiveness of hormonal contraceptives.

Participation in this lumacaftor and ivacaftor combination therapy study requires a commitment from the subject and his/her partner to use at least 1 effective method of birth control. Acceptable methods of contraception for participants of this study and their partners are listed below. Methods of contraception should be in successful use from at least 14 days

before the first dose of study drug (unless otherwise noted) and until 90 days following the last dose of study drug.

Contraception for the couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
- If the male is infertile (e.g., bilateral orchiectomy). Infertility may be documented through examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound before the first dose of the study drug.
- If the female is of non-childbearing potential, per the following:
  - Documented hysterectomy or a bilateral oophorectomy/salpingo-oophorectomy.
  - Note: All other female subjects who have had their first menstrual period (including subjects with tubal ligations and subjects who do not have a documented hysterectomy) from the time of the Day 1 Visit, or at any point through the Safety Follow-up Visit, will be considered to be of childbearing potential.

Acceptable Contraceptive Methods:

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

- Vasectomy 6 months or more previously, with a negative post-vasectomy semen analysis for sperm.
- Condom with spermicide (either as a single product if commercially available and/or allowed according to local regulations; otherwise condom and spermicide as separate products). Local regulations may require use of an additional acceptable method of contraception.

Acceptable contraceptive methods for **female subjects** include the following:

- Bilateral tubal ligation performed at least 6 months previously.
- Continuous use of an intrauterine device (non-hormone-releasing) for at least 90 days.
- Barrier contraception (such as diaphragm, cervical cap, or female condom) with spermicide. Local regulations may require use of an additional acceptable method of contraception.
- Note: Hormonal contraceptives, including oral, injectable, transdermal, and implantable, will not be considered as an effective method; however, female subjects are not required to discontinue hormonal contraceptives.

Acceptable contraceptive methods for **female partners** of male subjects:

- Bilateral tubal ligation performed at least 6 months previously.
- Continuous use of an intrauterine device for at least 90 days.

- Barrier contraception (such as diaphragm, cervical cap, or female condom) with spermicide. Local regulations may require use of an additional acceptable method of contraception.
- Hormonal contraceptives, if successfully used for at least 60 days.

Additional notes:

- Female condom cannot be used with male condom (as a double method of contraception) due to risk of tearing.
- Male and female subjects who are not sexually active must agree to follow the contraceptive requirements of this study if they become sexually active with a partner of the opposite sex.
- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.
- Male subjects must not donate sperm after the first dose of study drug, throughout the study, and for 90 days following the last dose of study drug.
- Female subjects and female partners of male subjects should not plan to become pregnant during the study through 90 days following the last dose of study drug.
- Female subjects should not nurse a child from the start of study drug dosing through 90 days following the last dose of study drug.

Unique situations that may not fall within the above specifications may be discussed with the Vertex medical monitor or authorized designee on an individual basis.

11.7.8.2 Pregnancy

Subjects will be counseled to inform the investigator of any pregnancy that occurs during study treatment and for 90 days after the last dose of study drug(s).

If a subject or the female partner of a male subject becomes pregnant while participating in the study, study drug must be permanently discontinued immediately. The investigator must notify the medical monitor and Vertex Global Patient Safety (GPS) within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form.

If confirmed to be on active drug, the subject or partner will be followed until the end of the pregnancy and the infant will be followed for 1 year after the birth, provided informed consent is obtained. A separate ICF (and assent form, if applicable) will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

12 STATISTICAL AND ANALYTICAL PLANS

This section presents a summary of the planned analyses for this protocol and for the integrated analysis of Study 109, Study 011B, and Study 110. Statistical analysis details will be provided in the Statistical Analysis Plan (SAP). A stable draft SAP will be available

before the first subject first dose in the current open-label rollover study, which will be finalized before the clinical data lock for the study.

12.1 Sample Size and Power

This is a rollover study that plans to enroll subjects from qualifying previous studies (Study 109 and Study 011B) who meet the inclusion and exclusion criteria for this study. Approximately 256 subjects are potentially eligible to be enrolled into Study 110: approximately 200 subjects from Study 109 and approximately 56 subjects from Study 011B, if eligible. Table 12-1 provides the 95% CIs assuming different incidence of CF lung (preferred term for pulmonary exacerbation) in CF subjects.

Table 12-1 95% Confidence Intervals Assuming Different Observed Incidences of CF lung (n = 256)

Observed CF lung incidence	95% Confidence Interval
0.1	(0.063, 0.137)
0.2	(0.151, 0.249)
0.3	(0.244, 0.356)
0.4	(0.340, 0.460)

12.2 Analysis Sets

For the Observational Cohort, all summaries will be based on all enrolled subjects from the observational cohort in the current study.

For the Treatment Cohort, the following analysis sets will be defined:

All Subjects Set includes all subjects from the treatment cohort in the current study.

Full Analysis Set (FAS): The FAS will include all subjects in the Treatment Cohort who are enrolled and exposed to any amount of study drug in Study 110, including subjects rolled over from Study 109 and subjects rolled over from Study 011B. The FAS treatment group assignment is shown in Table 12-2; the treatment group will be as randomized/enrolled in the previous study.

Table 12-2 FAS Treatment Group Assignment

Treatment Groups	Description
LUM 200 mg q12h + IVA 250 mg q12h/ LUM q12h + IVA q12h	Subjects randomized/enrolled to LUM 200 mg q12h + IVA 250 mg q12h in the previous studies (Study 109 or Study 011B) and enrolled and dosed in Study 110[a]
Placebo/LUM q12h + IVA q12h	Subjects randomized to LUM 200 mg q12h + IVA 250 mg q12h matching placebo in Study 109 and enrolled and dosed in Study 110[a]

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

[a] Subjects who turn 12 years of age in the previous study or Day 1 of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h on Day 1. Subjects who turn 12 years of age after the Day 1 Visit of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h at their next scheduled visit.

Safety Set: The Safety Set will include all subjects in the Treatment Cohort who are exposed to any amount of study drug in Study 110. The safety treatment group will be as treated in the previous study.

Study 109 Rollover Set (109ROS): The Study 109 Rollover Set will include subjects rolled over from Study 109 and exposed to any amount of study drug in Study 110. Analysis based on 109ROS will be analyzed by Study 109 randomized treatment arms.

For the integrated analysis, the following analysis sets will be defined:

Integrated All Subjects Set includes all subjects from Study 109 and Study 011B. All subject data listings for the Treatment Cohort will be referenced using the Integrated All Subject Set, unless otherwise specified.

Integrated Full Analysis Set (IFAS) includes all subjects who are randomized and exposed to any amount of study drug in Study 109 or enrolled and exposed to any amount of study drug in Study 011B. The treatment group will be the same as that for Study 110 FAS.

Integrated Safety Set includes all subjects who are exposed to any amount of study drug in previous study. The treatment group will be the same as Study 110 Safety Set.

Study 109 Full Analysis Set (109FAS) includes all subjects who are randomized and exposed to any amount of study drug in Study 109. The treatment group will be the randomized treatment group in Study 109.

Other Analysis Sets

All subjects from Study 109 and subjects from the Study 011B LCI Substudy will have LCI measurements and the following analysis sets are defined to provide related summaries:

- **LCI Analysis Set** is a subset of FAS including subjects rolled over from Study 109 and subjects rolled over from the Study 011B LCI Substudy, who are enrolled and exposed to any amount of study drug in Study 110. The treatment group will be as randomized/enrolled in the previous study.

- **Integrated LCI Analysis Set** is a subset of IFAS including all subjects who are randomized and exposed to any amount of study drug in Study 109 or enrolled and exposed to any amount of study drug in Study 011B and consent to the Study 011B LCI Substudy. The treatment group will be the same as LCI Analysis Set.

[redacted]

12.3 Analysis Periods

Three different dosing periods will be used:

Current Dosing Period refers to the period starting with the initial dose of study drug in Study 110 to the last dose of study drug in Study 110.

Cumulative Dosing Period refers to the period starting with the initial dose of study drug in the previous study to the last dose of study drug in Study 110.

Active Dosing Period refers to the period starting with the initial dose of active treatment to the last dose of active treatment in Study 110.

Within each of the above dosing periods, safety analysis will be based on the treatment-emergent period, which starts from the start of the dosing period to 28 days (inclusive) after the last dose of the dosing period.

Handling of the data during the gap between the previous study and the rollover study will be detailed in the SAP.

12.4 Statistical Analysis

12.4.1 General Considerations

For the Observational Cohort, summaries will only be provided for the disposition, demographic and baseline characteristics, and SAEs. Summaries will be provided based on all enrolled subjects in that cohort.

For the Treatment Cohort, analyses will be repeated for current dosing period, cumulative dosing period (efficacy only), and active dosing period as shown in Table 12-3. All analyses will be provided using all data, regardless of whether the subjects turn 12 years of age and subsequently switch to LUM 400 mg q12h/IVA 250 mg q12h, to examine the treatment strategy, which includes the age-based dose regimen switch. [redacted]

[redacted]

Table 12-3 Analysis of Efficacy and Safety in Different Dosing Periods

Period	Efficacy	Safety
Current Dosing Period	X	X
Cumulative Dosing Period	X	None
Active Dosing Period	X	X

- Efficacy analysis (except those related to pulmonary exacerbations, LCI, [redacted]) will be based on the FAS for the current dosing period, and based on the IFAS for the cumulative dosing period and the active dosing period.
  - Pulmonary exacerbation-related analysis for the active dosing period will be based on 109FAS by treatment group. The placebo-controlled period for subjects randomized to the placebo arm will be analyzed separately.
  - LCI related analysis will be based on the LCI Analysis Set for the current dosing period, and based on the Integrated LCI Analysis Set for the cumulative dosing period and the active dosing period.

[redacted]

- Safety analysis will be based on the Safety Set for the current dosing period, and based on the Integrated Safety Set for the active dosing period.

All subject data listings for the Treatment Cohort will be referenced using the Integrated All Subjects Set, unless otherwise specified.

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

Categorical variables will be summarized using counts and percentages.

Baseline: The baseline value of each dosing period is defined as the most recent measurement before intake of the first dose of the corresponding dosing period, except if specified otherwise.

- For LCI-related parameters, the values at each visit will be the value provided by the LCI vendor based on the triplicates. The baseline of LCI will be the most recent non-missing value before the first dose of study drug in each dosing period.
- For ECG, the baseline will be defined as the average of the 3 pretreatment measurements on Day 1 for each dosing period.

- For sweat chloride, the values at each visit will be based on the averaged measurements from left and right arms. The baseline for cumulative dosing period will be the baseline from the previous study, i.e., average of the values at screening and the pretreatment measurement on Day 1 from the previous study. If only 1 pre-first dose measurement of sweat chloride is available, that measurement will be considered the baseline. The baseline for the current dosing will be the value at the most recent visit before the first dose of Study 110. The baseline for active dosing period, for subjects on the active arm from Study 109 and subjects from Study 011B, will be the baseline from the previous study, i.e., the average of the values at screening and the pretreatment measurement on Day 1 from the previous study; for subjects on the placebo arm from Study 109, the baseline will be the baseline from the current study, i.e., the most recent measurement before the first dose of Study 110.

12.4.2 Background Characteristics

12.4.2.1 Subject Disposition

Number and percentage of subjects in the following categories will be summarized for the Treatment Cohort, for current dosing period, cumulative dosing period, and active dosing period separately:

- For current dosing period:
  - All Subject Set
  - FAS
  - Safety Set
  - Study 109 ROS
- For cumulative dosing period and active dosing period:
  - Integrated All Subject Set
  - IFAS
  - Integrated Safety Set
  - Study 109 FAS
- For all 3 dosing periods:
  - Completed treatment
  - Prematurely discontinued the treatment and the reasons for discontinuations
  - Completed study
  - Prematurely discontinued the study and the reasons for discontinuations
  - Last completed on-treatment scheduled visit for subjects who discontinued treatment

Similar disposition tables will be provided for

- Subjects from Study 109 and the Study 011B LCI Substudy: Based on the LCI Analysis Set for the current dosing period and based on the Integrated LCI Analysis Set for the cumulative dosing period and active dosing period.

[redacted]

Number and percentage of subjects in the following categories will be summarized for the Observational Cohort:

- Enrolled
- Completed Long-term Follow-up Visits (telephone contacts)
- Prematurely discontinued the study during the Long-term Follow-up and the reasons for discontinuations

12.4.2.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for current dosing period, cumulative dosing period, and active dosing period for the Treatment Cohort and separately for the Observational Cohort.

12.4.2.3 Prior and Concomitant Medications

Number and percentage of subjects with prior medication and concomitant medications will be summarized for current dosing period, cumulative dosing period, and active dosing period:

- **Prior medication:** medication continued or newly received before initial dosing for each dosing period.
- **Concomitant medication**: medication continued or newly received in the treatment-emergent period for each dosing period.
- **Post-treatment medication:** medication continued or newly received after the end of the treatment-emergent period for each dosing period.

Handling of all ongoing or new medications at, or after, completion of treatment in Study 109 and Study 011B through the initial dose of study drug administered in Study 110, will be detailed in the SAP.

Handling of missing dates (e.g., missing start/end date) will be discussed in the SAP.

12.4.2.4 Study Drug Exposure

Study drug exposure will be summarized for current dosing period, cumulative dosing period, and active dosing period separately.

Duration of exposure for each dosing period is defined as: last dose date of the dosing period − first dose date of the dosing period + 1 day, regardless of unplanned interruptions for the summary of drug exposure for all 3 dosing periods, and regardless of the 2-week

planned interruption for subjects from Study 011B for the summary of study drug exposure for the cumulative dosing period and the active dosing period. If the last dose date of study drug is missing, the subject's treatment discontinuation or completion date will be used for analysis purpose.

Duration/cumulative duration of study drug exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). Additionally, the sum of a subject's duration/cumulative duration of treatment exposure (expressed in subject years) will be provided. Duration/cumulative duration of exposure will also be summarized as a categorical variable:

- for the current dosing period: ≥1 dose of study drug to <24 weeks, ≥24 to <48 weeks, ≥48 to <72 weeks, ≥72 to <96 weeks, ≥96 weeks; and
- for the cumulative dosing period and the active dosing period: ≥1 dose of study drug to <24 weeks, ≥24 to <48 weeks, ≥48 to <72 weeks, ≥72 to <96 weeks, ≥96 weeks to <120 weeks, and ≥120 weeks).

12.4.2.5 Study Drug Compliance

Study drug compliance will be summarized for current dosing period, cumulative dosing period, and active dosing period separately.

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

Percent of tablets taken will be calculated as follows: 100 × (total number of tablets administered) / (4 × [duration of study drug exposure in days + total number of days study drug interrupted after last dose, if any]). Subjects having calculated percent of tablets taken >100% will be considered as 100% in percent of tablets taken.

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

12.4.3 Efficacy Analysis

Assessment of the efficacy and durability of long-term treatment with lumacaftor in combination with ivacaftor in the Treatment Cohort is a secondary objective of this study.

For continuous efficacy variables: Lung clearance index ($LCI_{2.5}$ and $LCI_{5.0}$) (for subjects rolled over from Study 109 and the Study 011B LCI Substudy), sweat chloride, $ppFEV_1$ (both absolute change and relative change), BMI and BMI-for-age z-score, weight and weight-for-age z-score, height and height-for-age z-score, CFQ-R respiratory domain, and

TSQM, raw values and absolute change (or relative change) from baseline, at each visit, will be summarized. Descriptive statistics including number of subjects (n), mean, SD, standard error (SE), median, minimum, and maximum will be provided. In addition, 95% CI of the mean will be presented.

For the analyses of LCI and $ppFEV_1$, a mixed-effect repeated-measure model (MMRM) will be fitted for the cumulative dosing period, including visits from the previous Study 109 and Study 011B and visits from the current Study 110 based on IFAS. In the MMRM models for the cumulative dosing period, the absolute change from baseline of the previous study (including all predose measurements at each visit in the cumulative dosing period, both on-treatment measurements and measurements after treatment discontinuation), will be included as the dependent variable; treatment group, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect with adjustment for previous study (Study 109 versus Study 011B), weight (<25 kg versus ≥25 kg), and $ppFEV_1$ severity (<90 versus ≥90), both as determined at screening in the previous study. In the analysis of LCI, baseline LCI value will also be included as a continuous covariate in the MMRM model. The result obtained from the model will be the treatment effect at each postbaseline visit. The estimated mean treatment effect, a 95% CI, and a 2-sided *P* value will be provided. The least squares (LS) means (95% CI) at each visit will be plotted by treatment group.

In the model, visit will be treated as a class variable, and an unstructured covariance matrix will be assumed to model the within-subject variability. This model imposes no assumptions on the correlational structure and is considered robust. If there is a convergence problem due to the unstructured covariance matrix, the unstructured covariance matrix will be replaced by compound symmetry in the primary analysis. Denominator degrees of freedom for the *F*-test for fixed effects will be estimated using the Kenward-Roger approximation.[65] With a mixed-effects model as the primary analysis model based on restricted maximum likelihood estimation and assuming that conditional on fixed and random effects, when data are missing at random, no imputation of missing data will be done.

Additional modeling for LCI and $ppFEV_1$ and similar analyses may be conducted for other continuous variables. Details will be provided in the SAP.

Pulmonary exacerbation-related endpoints will be analyzed based on 109FAS for the active dosing period and separately for the placebo-controlled period for subjects randomized to placebo group in Study 109.

Number of Pulmonary Exacerbations (Subjects From Study 109 Only)

The number of pulmonary exacerbations, both on-treatment events and events after treatment discontinuation, will be analyzed based on 109FAS using a negative binomial regression model. The model will include treatment, weight (<25 kg versus ≥25 kg) and $ppFEV_1$ severity (<90 versus ≥90), both as determined at screening in Study 109. The data during the placebo-controlled period for subjects randomized to the placebo group in Study 109 will be analyzed using a similar negative binomial regression model without the treatment in the model.

The annualized rate of pulmonary exacerbation, defined as number of pulmonary exacerbations divided by total exposure, will be summarized and plotted using boxplot.

To further examine whether the treatment effect on pulmonary exacerbation was maintained over time, the annualized event-rate, separately for the previous study (Study 109) and the current study (Study 110), will be provided by treatment arm.

Event of Pulmonary Exacerbation (Subjects From Study 109 Only)

The summary statistics including number of subjects (n) and percent will be provided. A bar chart of incidence of pulmonary exacerbations will be provided.

Time-to-First Pulmonary Exacerbation (Subjects From Study 109 Only)

Time-to-first pulmonary exacerbation will be analyzed and plotted using the Kaplan-Meier estimates. Both on-treatment event and event after treatment discontinuation will be considered. Of subjects enrolled in the Treatment Cohort of Study 110, one without a pulmonary exacerbation before withdrawal from the current study is considered censored at the time of withdrawal, and a subject without an exacerbation who completes the efficacy analysis period is considered censored at the end of the efficacy analysis period. Of subjects not enrolled in the Treatment Cohort of Study 110, one without a pulmonary exacerbation before withdrawal from the previous study is considered censored at the time of withdrawal, and one without a pulmonary exacerbation who completes the previous study is considered censored at the end of the efficacy analysis period of the previous study.

The analysis will be provided for the active dosing period based on 109FAS by treatment arms. For subjects randomized to placebo group in Study 109, time-to-first pulmonary exacerbation during the placebo-controlled period will be analyzed similarly.

Rate of Change in LCI (Subjects From Study 109 and the Study 011B Substudy Only) and $ppFEV_1$

Linear mixed-effects (LMM) analyses will be conducted to estimate the overall rate of change in LCI ($LCI_{2.5}$ and $LCI_{5.0}$) and $ppFEV_1$ during the active dosing period based on IFAS. The dependent variable will be postbaseline value in LCI and postbaseline value in $ppFEV_1$, respectively, and the model will include treatment groups as the fixed effect, random intercept and slope for treatment duration (in years), and adjustment for previous study (Study 109 versus Study 011B), weight (<25 kg versus ≥25 kg) and $ppFEV_1$ severity (<90 versus ≥90), both as determined at screening in the previous study. In the analysis of rate of change in LCI, the model will further adjust for baseline LCI as a continuous variable. The rate of change will be reported as an annualized rate of change; 95% CI will also be provided. Measurements at, and after, Week 2 of the active dosing period, will be included to estimate the rate of change. Depending on the results from Study 109 and Study 011B, different starting times may be explored if the treatment plateau is not reached by the specified time.

[redacted]

12.4.4 Safety Analysis

Evaluating safety of long-term treatment with lumacaftor in combination with ivacaftor in the Treatment Cohort is the primary objective of this study. The overall safety profile of the combination treatment will be assessed in terms of the following:

- Treatment-emergent AEs (TEAEs)
- Clinical laboratory values
- ECGs
- Vital signs
- Pulse oximetry
- Ophthalmological examinations
- Spirometry

Only a descriptive analysis of safety will be performed (i.e., no formal between-treatment statistical testing will be performed).

12.4.4.1 Adverse Events

For the Observational Cohort, a summary table will be presented for all SAEs.

For the Treatment Cohort, TEAEs will be summarized for current dosing period based on Study 110 Safety Set, and for the active dosing period based on Integrated Safety Set.

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

- **TEAE:** any AE that increased in severity or newly developed during the treatment-emergent period.
- **Post-treatment AE:** any AE that increased in severity or newly developed after the treatment-emergent period.

Handling of AEs, that are ongoing or newly developed at, or after, the completion of treatment in Study 109 and Study 011B through the initial dose of study drug administration in Study 110, will be detailed in the SAP.

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

An overview of the TEAE profile will be provided, including total number of TEAEs, with number and percentage of subjects for the following categories: (1) All TEAEs, (2) Grades 3/4 TEAEs, (3) TEAEs by relationship, (4) TEAEs by maximum severity, (5) TEAEs leading to treatment interruption, (6) TEAEs leading to treatment discontinuation, (7) Serious TEAEs, (8) Related serious TEAEs, and (9) TEAEs leading to death. A summary of number and percentages of subjects, as well as number of events per 100 patient-years (number of events adjusted for the total duration of exposure), will be provided.

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

- All TEAEs
- Grades 3/4 TEAEs
- TEAEs by relationship

- TEAEs by maximum severity
- TEAEs leading to treatment interruption
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- Related serious TEAEs
- TEAEs leading to death
- Frequently reported TEAEs

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

Additional summary tables will be presented for TEAEs showing number and percentage of subjects with

- Any TEAEs by PT
- Frequently reported TEAEs by PT

In addition, 3 listings containing individual subject AE data for all deaths, SAEs, and permanent discontinuations due to AE will be provided.

[redacted]

12.4.4.2 Clinical Laboratory Assessments

A summary of raw values and change from baseline values at each visit will be provided for the continuous laboratory results in SI units for current dosing period based on Study 110 Safety Set, and for the active dosing period based on the Integrated Safety Set. For each of the LFTs, mean values will be plotted against visit by treatment arm.

The number and percentage of subjects with shift changes from baseline (normal/missing, high, low, according to the reference range), based on the worst on-treatment laboratory evaluation, will be tabulated.

For subjects with at least 1 potentially clinically significant (PCS) event during the treatment-emergent period, summaries will be presented for each elevation category using number and percentage of subjects as well as number of elevations per 100 patient-year

(number of elevations adjusted for the total duration of exposure). The PCS criteria will be provided in the SAP.

A listing of subjects with elevated LFT results during the treatment-emergent period will be presented including all parameters of the liver function and assessment at all visits.

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

12.4.4.3 Electrocardiogram

A summary of raw values and change from baseline values at each visit will be provided for current dosing period based on Study 110 Safety Set, and for the active dosing period based on the Integrated Safety Set for the following standard digital ECG measurements: PR, QT, QTc intervals, QRS, and HR. Mean QTcF values will be plotted against visit.

For subjects with at least 1 PCS event during the treatment-emergent period, the number and percentage of subjects with PCS per 100 patient-year (number of PCS adjusted for the total duration of exposure) will be tabulated. The PCS criteria will be provided in the SAP.
A listing of subjects with PCS events during the treatment-emergent period will be presented, including all parameters and assessments at all visits.

The number and percentage of subjects with shift changes from baseline, based on the worst on-treatment overall ECG evaluation, will be tabulated.

12.4.4.4 Vital Signs

A summary of raw values, and change from baseline values at each visit, will be provided for current dosing period based on Study 110 Safety Set, and for the active dosing period based on the Integrated Safety Set for the following vital signs variables: systolic and diastolic blood pressure (mm Hg), body temperature (°C), HR (beats per minute), and respiratory rate (breaths per minute).

For subjects with at least 1 PCS event during the treatment-emergent period, the number and percentage of subjects and number of PCS per 100 patient-year (number of PCS adjusted for the total duration of exposure) will be tabulated. The PCS criteria will be provided in the SAP. A listing of subjects with PCS events during the treatment-emergent period will be presented, including all parameters and assessments at all visits.

The number and percentage of subjects with shift changes from baseline (normal/missing, high, or low according to the reference range) based on the worst on-treatment vital signs evaluation will be tabulated.

12.4.4.5 Pulse Oximetry

For the pulse oximetry measurements, a summary of raw values and change from baseline values will be provided for current dosing period based on Study 110 Safety Set, and for the active dosing period based on the Integrated Safety Set at each scheduled time point for the percent of oxygen saturation by pulse oximetry. In addition, the mean value at each visit will be plotted for the percent of oxygen saturation.

The number and percentage of subjects with shift changes from baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the treatment-emergent period will be tabulated based on the Safety Set.

12.4.4.6 Ophthalmological examinations

For the analysis of slit lamp lens, the number and percentage of subjects with shift changes from baseline (normal versus abnormal) will be tabulated for the current dosing period based on Study 110 Safety Set, and active dosing period based on the Integrated Safety Set at each scheduled time point. Ophthalmological examination findings will be presented as a data listing.

12.4.4.7 Spirometry

Analysis of Predose Spirometry at Each Postdose Visit

Spirometry data will be summarized descriptively for the predose assessment at each postdose visit, for the current dosing period based on Study 110 Safety Set, and the active dosing period separately, based on the Integrated Safety Set:

- Number and percentage of subjects with ≥5 percentage points decrease, or ≥10 percentage points decrease in absolute change from baseline in $ppFEV_1$ at each visit
- Number and percentage of subjects with ≥5% decrease, or ≥10% decrease in relative change from baseline in $ppFEV_1$ at each visit
- Number and percentage of subjects with ≥0.05 L decrease, or ≥0.10 L decrease in absolute change from baseline in FEV_1 at each visit
- Number and percentage of subjects with ≥5% decrease, or ≥10% decrease in relative change from baseline in FEV_1 at each visit

Subjects with ≥5 percentage points decrease in absolute change from baseline in $ppFEV_1$ or ≥0.05 L absolute change from baseline in FEV_1 at any visit will be listed. The listing will include raw values and absolute/relative changes from baseline in $ppFEV_1$ and FEV_1 at all visits.

Analysis of Serial Spirometry

Based on the Integrated Safety Set for the active dosing period and based on the Study 110 Safety Set for the current dosing period, raw values and absolute change from predose assessment in $ppFEV_1$ and FEV_1 will be summarized by visit and by time point:

The mean values (95% CI) will be plotted against visit and time points. The number and percentage of subjects with a decline ≥5, ≥10, ≥15, and ≥20 percentage points in the absolute change from the predose value in $ppFEV_1$ will be summarized by visit and time point.

12.4.4.8 Physical Examination

PE findings will be presented as a data listing.

12.4.4.9 Other Safety Analysis

Not applicable

12.4.5 Interim and IDMC Analyses

12.4.5.1 Interim Analysis

One interim analysis (IA) will be conducted for the Treatment Cohort when all subjects have completed the Week 24 Visit. Details of the analyses will be described in the IA SAP.

Additional IAs may take place at any other time during the study if (1) warranted by the ongoing data, (2) needed for regulatory purposes, and/or (3) deemed necessary by the internal Vertex team.

12.4.5.2 IDMC Analysis

Details of the IDMC (Section 8.1.4) analysis will be provided in the IDMC Analysis Plan.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

Study assessments including laboratory tests, ECGs, PEs, and vital signs, will be assessed and those deemed a clinically significant worsening from baseline 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 clinical status of the subject indicates a life-threatening AE.

13.1.1.3 Documentation of Adverse Events

All ongoing or newly developed AEs at, or after, completion of treatment in Study 109 or Study 011B will be collected until the following time points:

- Withdrawal of consent or through the Safety Follow-up Visit (NOTE: only SAEs will be collected for the Observational Cohort)
- For enrolled subjects who do not have a Safety Follow-up Visit: 28 days after the last dose of study drug

All subjects will be queried, using non-leading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms will be identified as 1 overall event or diagnosis. All AEs for enrolled subjects will be recorded in the eCRF and source document. 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 non-serious 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 2012). 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 experience that places the subject, in the view of the investigator, at immediate risk of death

13.1.1.5 Adverse Event Causality

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

Table 13-2 Classifications for AE Causality

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

13.1.1.6 Study Drug Action Taken

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

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

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

13.1.1.7 Adverse Event Outcome

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

Table 13-4 Classifications for Outcome of an AE

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

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

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

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

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

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

13.1.2.2 Documentation of Serious Adverse Events

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

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

13.1.2.3 Reporting Serious Adverse Events

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

Please send completed SAE Forms to Vertex Global Patient Safety via
Email: [redacted] (Preferred Choice)
Or via Fax: [redacted]
Contact Telephone: [redacted]

13.1.2.4 Expedited Reporting and Investigator Safety Letters

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

It is the responsibility of the investigator or designee to promptly notify the local IRB/local IEC of all unexpected serious adverse drug reactions involving risk to human subjects.

13.2 Administrative Requirements

13.2.1 Ethical Considerations

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

13.2.2 Subject Information and Informed Consent

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

13.2.3 Investigator Compliance

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

When circumstances require an immediate departure from procedures set forth in the protocol, the investigator will contact Vertex to discuss the planned course of action. If possible, contact will be made before the implementation of any changes. Any departures from 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 eCRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers and access to subject names linked to such numbers shall be limited to the site and the study doctor and shall not be disclosed to Vertex. As required by applicable laws and regulations in the countries in which the study is being conducted, the investigator will allow Vertex and/or its representatives access to all pertinent medical records to allow for the verification of data gathered in the eCRFs/SAE forms and the review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/IEC, may also request access to all study records, including source documentation, for inspection.

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

13.2.6 Record Retention

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

13.2.7 Study Termination

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

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

- Subject or investigator noncompliance

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

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

13.3 Data Quality Assurance

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

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each enrolled subject will be entered into an eCRF 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 eCRF 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 eCRFs/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 eCRFs/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 eCRFs on the subjects for which they are responsible.

An eCRF 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 eCRF. Source documentation supporting the eCRF 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 eCRF 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 eCRFs, including any changes made to the eCRFs, to endorse the final submitted data for the subjects for whom the investigator is responsible.

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

13.6 Publications and Clinical Study Report

13.6.2 Clinical Study Report

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

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX15-809-110	Version #: 2.0	Version Date 15SEP2015
Study Title: A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation		

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

[redacted]

15.2 Investigator Signature Page

Protocol #: VX15-809-110	Version #: 2.0	Version Date 15SEP2015
Study Title: A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation		

I have read Protocol VX15-809-110, Version 2.0 and agree to conduct the study according to its terms. I understand that all information concerning lumacaftor/ivacaftor and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date