1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 4, Open-label Treatment, Randomized, Multicenter, 2-arm, Parallel-group, Pilot Study of Adherence to Lumacaftor/Ivacaftor in CF Subjects Homozygous for the *F508del-CFTR* Mutation

Vertex Study Number: VX15-809-114

[redacted]

Date of Protocol: 19 Oct 2016 (Version 2.0)

Replaces Version 1.0, dated 18 Dec 2015

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

2 PROTOCOL SYNOPSIS

Title A Phase 4, Open-label Treatment, Randomized, Multicenter, 2-arm, Parallel-group, Pilot Study of Adherence to Lumacaftor/Ivacaftor in CF Subjects Homozygous for the *F508del-CFTR* Mutation

Brief Title A Pilot Study to Evaluate the Use of Smart Adherence Technology to Measure Lumacaftor/Ivacaftor Adherence in CF Subjects Homozygous for the *F508del-CFTR* Mutation

Clinical Phase and Clinical Study Type Phase 4, Adherence

Objectives

Primary

To evaluate the impact of smart adherence technology for monitoring LUM/IVA adherence rates among subjects 16 years of age and older with CF who are homozygous for the *F508del-CFTR* mutation

Secondary

To collect subject and physician feedback on the use of smart adherence technology to monitor LUM/IVA adherence

Endpoints

Primary Endpoint

Mean percentage adherence to LUM/IVA treatment over 48 weeks

Secondary Endpoints

- Mean percentage adherence to LUM/IVA treatment over 24 weeks
- Mean percentage adherence to LUM/IVA treatment from Week 25 through Week 48
- Proportion of subjects with ≥80% LUM/IVA adherence over 24 weeks
- Proportion of subjects with ≥80% LUM/IVA adherence over 48 weeks
- Proportion of subjects with ≥80% LUM/IVA adherence from Week 25 through Week 48
- Proportion of subjects with a non-physician-directed LUM/IVA interruption ≥72 hours over 48 weeks
- Number of non-physician-directed LUM/IVA interruptions ≥72 hours over 48 weeks
- Time to the first non-physician-directed LUM/IVA interruption ≥72 hours over 48 weeks

[redacted]

Number of Subjects

Approximately 75 subjects will be enrolled.

Study Population

Male and female subjects 16 years of age and older with CF who are homozygous for the *F508del-CFTR* mutation

Investigational Drug

Active substance: LUM and IVA (fixed-dose combination [FDC] with LUM and IVA)

Activity: CFTR corrector and potentiator (chloride ion secretion)

Strength and Route of Administration: 200-mg LUM/125-mg IVA (200/125 mg) film-coated tablets for oral administration

Dose Regimen: LUM 400 mg/IVA 250 mg every 12 hours (q12h)

Smart Adherence Technology

- Smart Pill Bottle, activated
- Smart Pill Bottle (control), de-activated alerts and feedback features

Study Duration

The total duration is approximately 56 weeks (up to 28 days for the Screening Period, 48 weeks for the Treatment Period, and 28 days (± 7 days) for Safety Follow-up Period, if applicable)

Study Design

This is a Phase 4, open-label, randomized, multicenter, 2-arm, parallel-group pilot study evaluating LUM/IVA adherence. Each study arm will include a smart technology with either active or inactive dosing alert features.

This study includes:

- Screening Period (Day −28 through Day −1)
- Treatment Period (Day 1 through Week 48)
- Safety Follow-up Visit at Week 52 (28 [± 7] days after the final dose of LUM/IVA

Approximately 75 subjects will be enrolled in this study. All subjects will receive LUM 400 mg/IVA 250 mg q12h through Week 48.

Subjects will be stratified by age (<23 versus ≥23 years of age) and forced expiratory volume in 1 second (FEV_1) severity (<70% versus ≥70% predicted) determined at the Screening Period and then randomized (2:1) to 1 of the following 2 smart adherence technology study arms:

- **Study Arm A:** Smart Pill Bottle, activated
- **Study Arm B:** Smart Pill Bottle (control), de-activated alerts and feedback features

Subjects will receive standardized education on the benefit of LUM/IVA, LUM/IVA adherence, and training on the use of the assigned smart adherence technology. During applicable study visits, subjects will complete adherence and technology satisfaction assessments. Physicians will also complete a technology satisfaction questionnaire adherence assessments.

Assessments

Adherence: Smart Adherence Technology-Reported Adherence

[redacted]

Safety: Adverse events, ophthalmologic examinations, clinical laboratory assessments, vital signs, physical examinations

[redacted]

Statistical Analyses

Statistical analysis details will be provided in the Statistical Analysis Plan (SAP).

The primary endpoint is the mean percentage adherence to LUM/IVA treatment over 48 weeks. Assuming a standard deviation (SD) of 8, a sample size of 50 subjects in Study Arm A and 25 in Study Arm B will have 80% power to detect a treatment difference of 5.6% between the means of the 2 arms using a 2-sided, 2-sample t-test at the 0.05 significance level.

The primary analysis for the primary endpoint variable will be based on an analysis of covariance (ANCOVA) with mean percentage adherence over 48 weeks as the dependent variable, Study arm as a fixed effect with covariates for age (<23 versus ≥23 years old), FEV_1 (<70% versus ≥70% predicted), [redacted], and sex (male versus female), at Screening. [redacted]

[redacted]

Summary statistics for each study arm will be provided. Primary and secondary analyses of adherence will be performed through smart technology generated data. A complementary analysis based on pill count and missing/interruption of dose will also be conducted. Summary of weekly adherence data will be provided; pattern of adherence over 48 weeks will be plotted and may be modeled using mixed effects models.

No interim analysis is planned for this study.

3 SCHEDULE OF ASSESSMENTS

Schedules of Assessments are shown in Table 3-1 (Screening Period) and Table 3-2 (Treatment Period and Safety Follow-up Visit).

All visits are to be scheduled relative to the Day 1 Visit.

Table 3-1 Screening Period Assessments – Study VX15-809-114

Assessment	Screening Period Day -28 to Day -1
Informed consent and assent (where applicable)	X
Inclusion and exclusion criteria review	X
Demographics	X
Height, weight, and BMI	X
Review of medical history (includes *CFTR* genotype)[a]	X
Ophthalmologic examination[b]	X
Prior and concomitant medications	X
Vital signs[c]	X
Physical examination[d]	X
Spirometry[e]	X
Serum pregnancy test (all female subjects of childbearing potential)[f]	X
Serum FSH[g]	X
Hematology[h]	X
Liver Function Testing[i]	X
[redacted]	
AEs and SAEs	Continuous from signing of ICF or assent (where applicable) through Safety Follow-up Visit

AE: adverse event; BMI: body mass index; CF: cystic fibrosis; *CFTR*: *CF transmembrane conductance regulator* gene; FSH: follicle-stimulating hormone; ICF: informed consent form; IVA: ivacaftor; LUM: lumacaftor; PE: physical examination; SAE: serious adverse event; [redacted]

[a] Genotype testing will be performed if this is not documented in medical history. CF genotyping can be waived with documented CFTR genotype (Section 11.5.2).

[b] An ophthalmologic examination will be conducted by either a licensed ophthalmologist or an optometrist for all subjects <18 years of age. The exam may be waived if there is documentation of an exam within 3 months of the date of informed consent (or assent, when applicable). Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination (Section 11.5.6).

[c] Vital signs will be assessed following a 5-minute rest in the seated or supine position.

[d] Physical examination of all body systems (Section 11.5.4).

[e] Spirometry may be performed pre- or postbronchodilator (Section 11.5.5).

[f] Any female subject initiating LUM/IVA combination therapy who is considered to be of childbearing potential should have a serum pregnancy test. Women of childbearing potential are defined as: female subjects after puberty unless they are postmenopausal for at least 1 year and have documented FSH levels within the postmenopausal reference range of the performing laboratory, or are surgically sterile.

[g] Serum FSH levels will be measured for any suspected postmenopausal female subjects with at least 12 months of continuous spontaneous amenorrhea.

[h] Blood samples will be collected for clinical laboratory assessments (Section 11.5.2).

[i] Liver function testing (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transpeptidase [GGT], alkaline phosphatase [ALP], and total bilirubin) must be performed at the scheduled visits (Section 11.5.2).

Table 3-2 Treatment Period and Safety Follow-up Visit Assessments – Study VX15-809-114

Event/Assessment	Day 1	Week 12	Week 24	Week 36	Week 48	Safety Follow-up Week 52[a]
Clinic visit	X	X	X	X	X	X
Vital signs[b]	X	X	X	X	X	X
Physical examination[c]					X	X[d]
Liver Function Testing[e]	X	X	X	X	X	X
Urine pregnancy test (all female subjects of childbearing potential)	X	X	X	X	X	X
Randomization[f]	X					
Standardized education on adherence	X					
Concomitant medications, treatments, and procedures	X	X	X	X	X	X
Smart Adherence Technology-Reported Adherence[g]		X	X	X	X	
[redacted]						
LUM/IVA drug count[i]		X	X	X	X	
Ophthalmologic examination[j]					X	
AEs and SAEs	Continuous from signing of ICF or assent (where applicable)					
LUM/IVA resupply	Every 3 months throughout study					

AE: adverse event; ICF: informed consent form; IVA: ivacaftor; IWRS: interactive web response system; LUM: lumacaftor; PE: physical examination; SAE: serious adverse event; [redacted]

[a] The Safety Follow-up Visit is 28 (± 7) days after the last dose of LUM/IVA (Section 8.1.3).
[b] Vital signs will be assessed following a 5-minute rest in the seated or supine position.
[c] Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.
[d] Required for subjects who do not begin commercial LUM/IVA after Week 48 only.
[e] Day 1 only blood draws will be collected before the first dose of LUM/IVA. Liver function testing (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transpeptidase [GGT], alkaline phosphatase [ALP], and total bilirubin) must be performed at the scheduled visits (Section 11.5.2).
[f] Randomization must occur after all inclusion and exclusion criteria are met and before the first dose of LUM/IVA. Randomization will be done through IWRS.
[g] Data will be collected for all subjects throughout the study in real-time. Subjects in Study Arm A will review data with physicians at study visits.
[redacted]
[i] LUM/IVA drug count will be collected at the end of specified study visits.
[j] See Section 11.5.6.

4 TABLE OF CONTENTS

List of Tables

List of Figures

5 INTRODUCTION

5.1 Background

Cystic fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality and at present, there is no cure. CF affects approximately 70,000 individuals worldwide.[1] Based on the size of the population, CF qualifies as an orphan disease.[2,3] Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is approximately 40 years.[4,5,6]

CF is caused by reduced quantity and/or function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein due to mutations in the *CFTR* gene. The CFTR protein is an epithelial chloride channel that aids in regulating salt and water absorption and secretion and pH balance in multiple organs, including the lungs, pancreas and other gastrointestinal organs, and sweat glands.[7] In people with CF, decreased CFTR chloride transport results in multisystem pathology. Although the disease affects multiple organs, progressive loss of lung function is the leading cause of mortality.[8]

More than 2000 mutations in the *CFTR* gene have been identified.[9] Based on the understanding of the molecular defects caused by *CFTR* mutations, 2 complementary approaches have been developed to address the decreased quantity and/or function of CFTR in order to enhance chloride transport in patients with CF. The first approach is to increase the quantity of CFTR delivered to the cell surface using small molecules known as CFTR correctors. The second approach is to increase the channel gating activity of CFTR at the cell surface using small molecules known as CFTR potentiators. One or both of these mechanisms may be necessary depending on the specific mutation. Because the channel gating activity of CFTR delivered to the cell surface by CFTR correctors can be enhanced by CFTR potentiators, together, CFTR correctors and potentiators provide complementary therapeutic approaches to improve chloride transport.

Lumacaftor (LUM) is a CFTR corrector, and ivacaftor (IVA) is a CFTR potentiator. LUM/IVA combination therapy is approved in the US, European Union, Canada, Australia, and Switzerland for the treatment of CF in patients 12 years of age and older who are homozygous for the F508del mutation, the most common mutation of the CFTR gene.

5.2 Study Rationale

CF is a chronic disease with challenges in long-term disease management. Inadequate treatment adherence is one of the most significant challenges in achieving effective health outcomes. An estimated 30-50% of medicines are not taken as recommended and adherence tends to decline after the first 6 months of treatment.[10]

Effective disease management relies on consistent adherence habits, yet adherence is an invisible, and often an unmonitored, expectation in routine care.[11] Discrepancies in clinical studies between objective (e.g., pharmacy refills) and self-reported measures of adherence (e.g., surveys, questionnaires) have led to development of smart adherence technology interventions (e.g., smart pill bottles). This study is designed to evaluate the impact of smart adherence technologies for supporting and monitoring LUM/IVA adherence rates among subjects 16 years of age and older with CF who are homozygous for *F508del*.

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the impact of smart adherence technologies for monitoring of LUM/IVA adherence rates among subjects 16 years of age and older with CF who are homozygous for the *F508del-CFTR* mutation

6.2 Secondary Objective

To collect subject and physician feedback on the use of smart adherence technology to monitor LUM/IVA adherence

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Mean percentage adherence to LUM/IVA treatment over 48 weeks

7.2 Secondary Endpoints

- Mean percentage adherence to LUM/IVA treatment over 24 weeks
- Mean percentage adherence to LUM/IVA treatment from Week 25 through Week 48
- Proportion of subjects with ≥80% LUM/IVA adherence over 24 weeks
- Proportion of subjects with ≥80% LUM/IVA adherence over 48 weeks
- Proportion of subjects with ≥80% LUM/IVA adherence from Week 25 through Week 48
- Proportion of subjects with a non-physician-directed LUM/IVA interruption ≥72 hours over 48 weeks
- Number of non-physician-directed LUM/IVA interruptions ≥72 hours over 48 weeks
- Time to the first non-physician-directed LUM/IVA interruption ≥72 hours over 48 weeks

[redacted]

8 STUDY DESIGN

8.1 Overview of Study Design

This is a Phase 4, open-label, randomized, multicenter, 2-arm, parallel-group pilot study evaluating LUM/IVA adherence. Each study arm will use a smart technology with either active or inactive dosing alert and feedback features.

This study includes:

- Screening Period (Day −28 through Day −1)
- Treatment Period (Day 1 through Week 48)
- Safety Follow-up Visit (28 [± 7] days after the final dose of LUM/IVA). Subjects who begin commercially available LUM/IVA combination therapy do not have to complete the Safety Follow-up Visit.

Figure 8-1 depicts a schematic of the study design. Approximately 75 subjects will be enrolled in this study. All subjects will receive LUM 400 mg/IVA 250 mg every 12 hours (q12h) through Week 48.

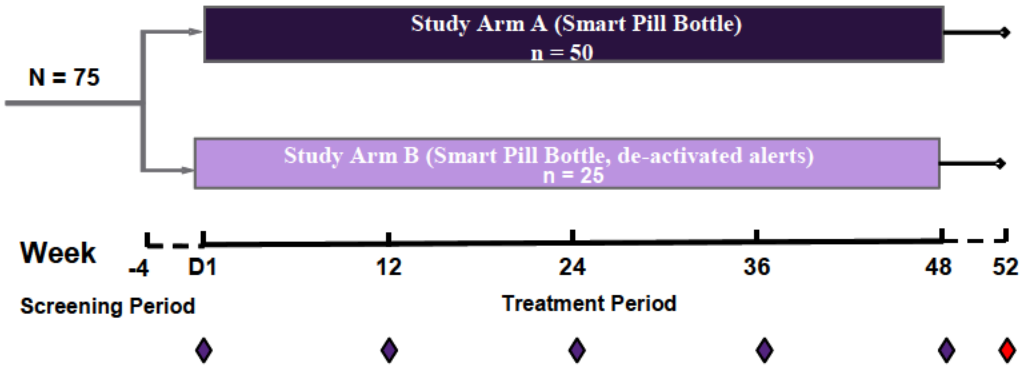
Subjects will be stratified by age (<23 versus ≥23 years of age) and forced expiratory volume in 1 second (FEV_1) severity (<70% versus ≥70% predicted) determined at the Screening Period and then randomized (2:1) to 1 of the 2 study arms:

- **Study Arm A:** Smart Pill Bottle, activated
- **Study Arm B:** Smart Pill Bottle (control), de-activated alerts and feedback features

Subjects will receive standardized education on the benefit of LUM/IVA, LUM/IVA adherence, and training on the use of the assigned smart adherence technology. During applicable study visits, subjects will complete adherence and technology satisfaction assessments. Physicians will also complete a technology satisfaction questionnaire. Table 3-2 provides a list of assessments by study visit.

All subjects will be required to complete study assessments for all scheduled visits. Subjects who prematurely discontinue LUM/IVA will complete a Safety Follow-up Visit (see Section 8.1.3).

Figure 8-1 Study Design



Study Visit; Safety Follow-up Visit; IVA: ivacaftor; LUM: lumacaftor
Notes: The Safety Follow-up visit is only required for subjects who do not begin commercially available LUM/IVA within 28 (± 7) days of the last dose of LUM/IVA.

8.1.1 Screening

Screening Visit assessments are listed in Table 3-1.

Screening will occur within 28 days before administration of LUM/IVA. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent or assent from each subject. If the time between screening and dosing exceeds 28 days as a result of unexpected operational delays (e.g., delayed drug shipment), then subjects do not require rescreening.

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

Subjects previously screened for another Vertex study may participate in this study if they meet the eligibility criteria. Screening data from the previous study may be used for this study if they were obtained within 28 days before administration of LUM/IVA.

Subjects who do not meet the eligibility criteria may not be rescreened, with the following exceptions, all of which require medical monitor approval:

- Subjects who met all eligibility criteria but had an intercurrent illness (e.g., upper respiratory infection with fever) in the 5 days before the first LUM/IVA dose that was properly evaluated and which resolved fully
- Subjects who met all eligibility criteria but are not able to obtain required documentation within the allotted screening window
- Subjects who met all eligibility criteria but transiently (for personal reasons) are unable to commit to all study procedures
- Subjects who met all eligibility criteria but are not randomized for administrative reasons (e.g., interactive web response system is temporarily inaccessible or nonfunctional or LUM/IVA is not available at the study site)

Any subject granted approval by the medical monitor for any of the exceptions listed above may have the screening window extended by 1 week before needing to undergo any rescreening assessments. If more than 35 days have elapsed from screening before first dose of LUM/IVA, all screening assessments need to be repeated. Repetition of any screening assessment that did not meet eligibility criteria is not permitted, unless there is clear evidence of a laboratory error (e.g., hemolysis of sample). In all cases, the medical monitor must authorize retesting.

8.1.2 Treatment Period

Treatment Period visits and assessments are listed in Table 3-2. Additional study visits may also occur as determined by the clinical site for routine care.

Subjects will be randomized at the Day 1 Visit to either Study Arm A or Study Arm B (described in Table 8-1). Each subject will be trained on the use of the assigned smart adherence technology and will use the technology throughout the Treatment Period. All subjects will receive LUM 400 mg/IVA 250 mg q12h throughout the Treatment Period.

Subjects who prematurely discontinue LUM/IVA treatment will complete a Safety Follow-up Visit (See Section 8.1.3).

Table 8-1 Study VX15-809-114 Smart Adherence Technology Study Arms

Smart Adherence Technology	Activated Features	Access to LUM/IVA Compliance Status	Number (n)
Smart Pill Bottle (Study Arm A)	Real-time dosing data transfer, electronic medication reminders/missed dose alerts (audio, visuals, texts, emails, phone calls)	Site staff and physicians, CRO, Vertex	50
Smart Pill Bottle, Control (Study Arm B)	Real-time dosing data transfer to CRO/Vertex only	CRO/Vertex only	25

CRO: contract research organization

The use of active smart adherence technologies (smart pill bottles) will provide subjects with objective and real-time feedback on dosing adherence, including reminders of upcoming or missed doses. Study physicians will access dosing adherence data and review them with subjects in Study Arm A at scheduled study visits. Subjects in Study Arm B will not receive any alerts, reminders, or real-time feedback on dosing adherence. Study Arm B will provide objective data on dosing adherence without influencing subjects to take a scheduled dose of LUM/IVA.

8.1.3 Follow-up

Subjects will have a Safety Follow-up Visit 28 (± 7) days after the last dose of LUM/IVA. Safety Follow-up Visit assessments are listed in Table 3-2. Subjects who begin commercial LUM/IVA before this visit do not have to complete the Safety Follow-up Visit.

8.1.4 Early Termination of Treatment

Subjects who prematurely discontinue LUM/IVA treatment for any reason (except withdrawal of consent or assent) and who do not begin commercial LUM/IVA will be asked to return to the clinical site 28 (± 7) days of their last dose of LUM/IVA for a Safety Follow-up Visit. Assessments performed at this visit will be the same for those in the Safety Follow-up Visit (Table 3-2).

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

8.2 Rationale for Study Design and Study Drug Regimens

8.2.1 Study Design

This pilot study is designed to provide information about the effect of smart adherence technologies on LUM/IVA treatment adherence. An estimated 30-50% of medicines are not taken as recommended and adherence tends to decline after the first 6 months of treatment.[11] Suboptimal adherence results in morbidity, mortality, preventable hospitalizations, a raised incidence of secondary complications,[9] and therefore societal and economic burdens.

Effective disease management relies on consistent adherence habits, yet adherence is an invisible, and often an unmonitored, expectation in routine care.[11] Discrepancies in clinical studies between objective (e.g., pharmacy refills) and self-reported measures of adherence (e.g., surveys, questionnaires) have led to development of smart adherence technology interventions

(e.g., smart pill bottles). These technologies allow patients to self-monitor medication adherence[10] through real-time electronic feedback via visual and auditory alarms, texts, emails, phone calls, and online dashboards. Smart adherence technologies enhance adherence by offering a method for CF patients and physicians to objectively monitor medication compliance[12] and to make long-term adherence both manageable and visible in daily routines.

This study is not designed or powered to assess a relationship between adherence and clinical outcomes. [redacted]

Subjects will be stratified by age (<23 versus ≥23 years of age) and FEV_1 severity (<70% versus ≥70% predicted) determined at the Screening Period and then randomized (2:1) to 1 of the 2 study arms described in Table 8-1.

A sample size of approximately 75 subjects is sufficient to detect a 5.6% difference between the study arms with 80% power.

8.2.2 Study Drug Dose and Duration

LUM/IVA Dose Rationale

Subjects will receive LUM 400 mg/IVA 250 mg q12h during the Treatment Period. This dose regimen has been approved in the US, European Union, Canada, and Australia for the treatment of CF in patients 12 years of age and older who are homozygous for the *F508del* mutation.

Study Duration Rationale

Treatment adherence to approved medications tends to decline after 6 months.[10] The 48-week study treatment duration was chosen to provide an adequate assessment of long-term adherence to LUM/IVA.

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 patients with CF. All assessments with the exception of the patient- and physician-reported outcomes and use of smart adherence technologies were routinely measured in the LUM/IVA combination program. Rationales for these assessments, the patient- and physician-reported outcomes, and use of smart adherence technologies are provided below.

Spirometry

FEV_1 as measured by spirometry is the most widely implemented standardized assessment to evaluate lung function in CF. This will be performed at the Screening Visit (See Section 11.5.5).

Ophthalmologic Examinations

Cases of noncongenital lens opacities have occurred in pediatric patients treated with ivacaftor, a component of LUM/IVA. Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating LUM/IVA treatment (See Section 11.5.6)

[redacted]

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 and/or legally appointed and authorized representative (e.g., parents or legal guardian) will sign and date an informed consent form (ICF) and where appropriate, an assent form.

2. Subject and/or legally appointed and authorized representative (e.g., parent or legal guardian) is willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Confirmed diagnosis of CF and homozygous for the *F508del-CFTR* mutation at Screening.
4. Subjects (male and female) will be aged 16 years and older on the date of informed consent or, where appropriate, assent.
5. FEV_1 ≥40% of predicted normal for age, sex, and height at Screening.

9.2 Exclusion Criteria

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

1. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering LUM/IVA to the subject, e.g., history of advanced liver disease.
2. Presence of moderate or severe hepatic impairment (Child-Pugh Class B or C).
3. Subjects currently receiving invasive mechanical ventilation.
4. Known history of alcohol or drug abuse in the past year, including but not limited to cannabis, cocaine, and opiates, as deemed by the investigator.
5. Any of the following abnormal laboratory values during screening:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × ULN
    - ALT or AST >3 × ULN with total bilirubin >2 × ULN
    - Glomerular filtration rate ≤30 mL/min/1.73 m2. This will be calculated by the Modification of Diet in Renal Disease study equation for subjects ≥18 years of age and calculated by the Counahan-Barratt equation for subjects aged 12 to 17 years.
6. Pregnant or nursing females (females of childbearing potential must have a negative pregnancy test at screening and Day 1).
7. Female subjects and female partners of male subjects who plan to become pregnant during Treatment Period or within 90 days following the last dose of LUM/IVA.
8. Sexually active subjects of reproductive potential who are not willing to follow the contraception requirements outlined in Section 11.5.7.1.
9. History of solid organ or hematological transplantation.
10. Ongoing or prior participation in an investigational drug study (including studies investigating LUM and/or IVA) within 30 days of screening
    - A washout period of 5 terminal half-lives of the previous investigational LUM/IVA or 30 days, whichever is longer
    - The duration of the elapsed time may be longer if required by local regulations.
11. Current use of commercial LUM/IVA combination therapy.

12. Subject, or close relative of the subject, is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site.

9.3 Study Restrictions

9.3.1 Prior and Concomitant Medications and Other Study Restrictions

Information regarding all prior and concomitant medications, including the subject's CF medications, other medications, and herbal and naturopathic remedies administered from 30 days before the Screening Period through the Safety Follow-up Visit will be recorded in each subject's source documents and electronic case report form (eCRF). For subjects who are screened but are not enrolled in the study, details of prior medications will be documented only in the subjects' source documents.

9.3.1.1 Drug Interactions

A nonexhaustive list of established and potentially significant drug interactions, including information on dosage adjustment, is provided in the approved product label for LUM/IVA (Orkambi®) (see study reference manual).

LUM is a strong inducer of CYP3A. Administration of LUM/IVA may decrease systemic exposure of medicinal products that are substrates of CYP3A, which may decrease therapeutic effect. Coadministration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended.

IVA is a substrate of CYP3A4 and CYP3A5 isoenzymes. Use of LUM/IVA with strong CYP3A inducers significantly reduces IVA exposure, which may reduce the therapeutic effectiveness of LUM/IVA. Therefore, coadministration with strong CYP3A inducers (e.g., rifampicin, St. John's wort [Hypericum perforatum]) is not recommended.

9.4 Removal of Subjects

Subjects may withdraw from the study at any time at their own request and subjects may be withdrawn at any time at the discretion of the treating physician or by Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. LUM/IVA treatment will be withdrawn for any female subject who has confirmed pregnancy and for any male subject whose female partner has a confirmed pregnancy. A subject may be withdrawn from the LUM/IVA 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 LUM/IVA combination therapy.
- A subject develops a life-threatening adverse event or a serious adverse event (SAE) that places him/her at immediate risk, and discontinuation of treatment with LUM/IVA and withdrawal from the study are deemed necessary
- A subject is noncompliant with the study requirements
- A subject has an increase in transaminases (ALT or AST), meeting criteria for interruption of LUM/IVA in Section 11.5.3.

A subject should be discontinued from the study for the following reason:

A subject on a transplant list undergoes lung transplantation

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 LUM/IVA, request that the subject return for a Safety Follow-up Visit, if applicable (see Section 8.1.4), and follow up with the subject regarding any unresolved AEs.

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

9.5 Replacement of Subjects

Subjects who withdraw or are withdrawn for nonsafety reasons during the LUM/IVA treatment period(s) may be replaced at Vertex's discretion.

10 STUDY DRUG AND SMART ADHERENCE TECHNOLOGIES ADMINISTRATION AND MANAGEMENT

10.1 Preparation and Dispensing

10.1.1 LUM/IVA

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

Blister pack tablets will be dispensed at the CRU into individual smart pill bottles by 2 operators, 1 of whom is a qualified pharmacist, and following national and local laws and regulations.

10.1.2 Smart Adherence Technologies

Table 8-1 describes the smart adherence technologies used in this study. Site pharmacists will distribute the assigned smart adherence technology to each subject with LUM/IVA.

Smart Pill Bottles

Subjects will be trained to use the smart pill bottle. Subjects in Study Arm A will receive additional instruction on the activated smart pill bottle monitoring features. A site pharmacist will repackage 3 months supply of LUM/IVA from blister packs into 4 Smart Pill Bottles. Three bottles will each store a 1-month supply of LUM/IVA. A fourth bottle will store an additional 7 days supply of LUM/IVA. Only 1 bottle will be activated at a time.

10.2 Administration

10.2.1 LUM/IVA

LUM/IVA fixed-dose tablet will be administered orally (Table 10-1).

Table 10-1 LUM/IVA Administration

All Subjects	Time	LUM/IVA (200/125 mg per tablet)
LUM 400 mg/IVA 250 mg q12h	AM	2 tablets
	PM	2 tablets

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

LUM/IVA should be administered within 30 minutes of consuming fat-containing food such as a standard CF high-fat, high-calorie meal or snack. LUM/IVA should be administered q12h (± 4 hours).

10.3 Method of Assigning Subjects to Treatment Groups

Approximately 75 subjects who meet the eligibility criteria will be randomized at 2:1 ratio to 1 of 2 study arms. All subjects will receive LUM/IVA. Subjects will be stratified by age (<23 versus ≥23 years of age) and FEV_1 severity (<70% versus ≥70% predicted) determined at the Screening Visit.

An interactive web response system (IWRS) will be used to assign subjects to study arms. Detailed instructions for randomization will be provided separately.

10.4 Dose Modification for Toxicity

If any unacceptable toxicity arises, a dose modification to LUM 200 mg/IVA 125 mg q12h for up to 7 days may be permitted after discussion with and approval by the medical monitor. Subjects who receive the LUM/IVA dose modification will be administered 1 tablet in the morning and 1 tablet in the afternoon and follow administration instructions as described in Section 10.2.

The medical monitor should be contacted before transitioning subjects back to LUM 400 mg/IVA 250 mg q12h.

10.5 Missed Doses

If subjects miss a dose and recall the missed dose within 6 hours, they should take their dose with food. If more than 6 hours have elapsed after their usual dosing time, they should skip that dose and resume their normal schedule for the following dose.

10.6 Study Drug Interruption

If LUM/IVA dosing must be interrupted due to AEs for more than 72 hours, the medical monitor must be notified. In these instances, LUM/IVA dosing may resume only after approval by the medical monitor. Specific instructions for interruption for elevated liver function test (LFT) levels are provided in Section 11.5.3.

10.7 Packaging and Labeling

At the start of the study, Vertex or designee will provide a labeled supply of LUM/IVA combination therapy to the central pharmacy via the treating physician's request.

LUM/IVA tablets will be supplied in blister cards by Vertex. A detailed dispensation plan, including dispensation into Smart Pill Bottles, will be provided in the Reference Manual.

LUM/IVA labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for LUM/IVA will be included in the Pharmacy Manual.

10.8 Study Drug and Smart Adherence Technology Supply, Storage, and Handling

LUM/IVA (200 mg/125 mg) will be supplied as pink film-coated tablets containing 200 mg LUM/125 mg IVA.

Blister cards must be stored under conditions noted in Table 10-2. While at the clinical site, the LUM/IVA must be stored in a secure and temperature-monitored area of limited access.

Instructions regarding the ordering, storage, and handling of LUM/IVA after dispensation to subjects will be provided to sites in the Reference Manual.

The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all LUM/IVA is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all LUM/IVA will be accounted for via the drug accountability forms as instructed by Vertex.

Table 10-2 Identity of LUM/IVA, Dosage, and Storage

Drug Name	Strength/Formulation/Route	Dosage	Storage Condition
LUM/IVA (200 mg/125 mg)	200 mg/125 mg tablet; oral	LUM 400 mg / IVA 250 mg q12h	≤30°C (≤86°F)

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

10.9 Drug and Smart Adherence Technology Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of (1) LUM/IVA received, (2) LUM/IVA dispensed to the subjects, (3) LUM/IVA returned by the subjects, (4) smart pill bottles received, (5) smart pill bottles dispensed to subjects, and (6) smart pill bottles returned by subjects. Subjects will be instructed to return all used and unused materials associated with LUM/IVA, including the assigned smart pill bottle, 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 LUM/IVA records and inventory throughout the study.

10.10 Disposal, Return, or Retention of Unused Drug

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

10.11 Blinding and Unblinding

This will be a study of adherence with a deactivated smart adherence technology control arm. LUM/IVA treatment will be given open-label.

11 ASSESSMENTS

11.1 Timing of Assessments

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

[redacted]

11.2 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, and weight. Based on the medical history, the subject will be assessed for any disqualifying medical conditions as specified in the inclusion and exclusion criteria. The medical history shall include a complete review of systems, past medical and surgical histories, and any allergies.

11.3 Adherence

11.3.1 Smart Adherence Technology-Reported Adherence

LUM/IVA adherence monitoring will occur throughout the Treatment Period using smart adherence technology. This technology will allow for collection of real-time LUM/IVA compliance by reporting LUM/IVA dosing times each time the smart pill bottles are opened. Only subjects in Study Arm A will review data with study physicians at the study visits listed in Table 3-2.

[redacted]

11.5 Safety

Safety evaluations will include AEs, clinical laboratory assessments, ophthalmologic examinations (for subjects <18 years of age), clinical evaluation of vital signs, and physical examinations (PEs).

11.5.1 Adverse Events

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

11.5.2 Clinical Laboratory Assessments

Blood samples and urine pregnancy tests will be analyzed at a central laboratory.

Blood and urine samples for clinical laboratory assessments will be collected as shown in Table 3-1 and Table 3-2. On Day 1, blood draws will be collected before the first dose of LUM/IVA. Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (Section 13.1.1).

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

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology
Total Bilirubin, direct bilirubin	Hemoglobin
Alkaline phosphatase	Erythrocytes:
Aspartate aminotransferase	Mean corpuscular hemoglobin
Alanine aminotransferase	Mean corpuscular hemoglobin concentration
Gamma-glutamyl transferase	Mean corpuscular volume
	Platelets
	Reticulocytes (absolute)
	Leukocytes
	Differential (absolute and percent):
	Eosinophils
	Basophils
	Neutrophils
	Lymphocytes
	Monocytes

Pregnancy (β-human chorionic gonadotropin) Tests for Females of Childbearing Potential: Serum (Screening only) and urine pregnancy tests will be performed at the site as specified in Table 3-1 and Table 3-2. The serum and urine pregnancy tests will be analyzed at the central laboratory. The urine pregnancy test on Day 1 must be negative before the first dose of LUM/IVA. Additional urine pregnancy tests may be required according to local regulations and/or requirements

If a urine pregnancy test is positive, all LUM/IVA dosing will stop and the pregnancy will be confirmed with a serum β-human chorionic gonadotropin test. If confirmed, the pregnancy will be reported and the subject will be permanently withdrawn from LUM/IVA (Section 11.5.7.2). If a pregnancy test is positive, the procedures outlined in Section 11.5.7.2 will be followed.

Follicle-stimulating hormone (FSH) (Screening Period only): Blood sample for FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous

spontaneous amenorrhea. Serum FSH levels must be within the postmenopausal reference range of the performing laboratory to be considered postmenopausal.

CFTR genotype (Screening Period only): *CFTR* genotyping will be performed to confirm the subject is homozygous for the *F508del-CFTR* mutation as documented in the subject's medical record. The results of the genotype must be obtained and reviewed during the Screening Period. CF genotyping can be waived if the subject has a documented genotype result from a previous Vertex study with a Screening Visit date of 01 June 2010 or later. Specific instructions will be provided in the Laboratory Manual.

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.

11.5.3 Liver Function Test Parameters

Mandatory Liver Function Testing

Liver function testing (ALT, AST, GGT, ALP, and total bilirubin) must be performed as noted in Table 3-1 and Table 3-2.

It is strongly recommended that subjects with new treatment-emergent ALT or AST elevations of >3 × ULN, total bilirubin >2 × ULN, or 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, AST and bilirubin levels, as clinically indicated. If ALT or AST is >5 × ULN, follow-up levels must be obtained within 7 ± 2 days.

If a subject cannot return to the site for liver function testing, a local laboratory may be used. Elevations in LFTs 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).

LUM/IVA Interruption

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

- ALT or AST >5 × ULN
- ALT or AST >3 × ULN, in association with total bilirubin >2 × ULN

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

Resumption of LUM/IVA

LUM/IVA may be resumed when transaminases return to baseline or are ≤2 × ULN, whichever is higher. Approval by the medical monitor is required before resumption of LUM/IVA. Upon

resumption of LUM/, transaminases should be assessed weekly for 4 weeks. If a protocol-defined transaminase elevation occurs within 4 weeks of rechallenge with the LUM/IVA, then LUM/IVA must be interrupted again as outlined above.

11.5.4 Physical Examinations and Vital Signs

Complete and symptom-directed physical examinations (PE) of body systems and vital signs assessment will be performed as listed in Table 3-1 and Table 3-2. Additional symptom-directed PEs and symptom-directed vital sign assessments can be performed at the discretion of the investigator or healthcare provider.

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

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

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

11.5.5 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines[16] as noted in Table 3-1 according to the additional guidelines that follow.

During the Screening Visit, a spirometry assessment may be performed pre- or postbronchodilator. The spirometry assessment will be recorded in the source documents as prebronchodilator or postbronchodilator.

The parameters listed below will be normalized using the standards of Wang et al.,[17] (for male subjects aged 12 through 17 years) or Hankinson et al.,[18] (for female subjects aged 16 years and older and male subjects aged 18 years and older).

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

11.5.6 Ophthalmologic Examination

Subjects who are <18 years old at Day 1 will undergo an ophthalmologic examination at the Screening and Week 48 visits. The exam will be performed by either a licensed ophthalmologist or optometrist, as noted in Table 3-1and Table 3-2, and will include:

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

The screening ophthalmologic examination must be completed and the results reviewed before enrollment. This examination does not have to be repeated if there is documentation of an examination that met protocol criteria within 3 months before the date of informed consent (or assent, when applicable) or if there is documentation of bilateral lens removal for the subject.

If a cataract or lens opacity is identified and determined to be clinically significant by the ophthalmologist or optometrist at the Screening examination, the subject (and the subject's parent or guardian if the subject is a minor) will be notified. 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.

If a cataract or lens opacity is identified and determined to be clinically significant by the ophthalmologist or optometrist after dosing, the subject will be notified. After discussion with the Principal Investigator and in collaboration with the medical monitor, the subject may elect to continue or discontinue LUM/IVA treatment. If the subject discontinues LUM/IVA treatment, the subject should complete the Safety Follow-up Visit. If the subject continues IVA treatment, more frequent ophthalmologic monitoring should be considered.

In addition, at screening, the following history will be obtained and documented for all subjects:

- History of steroid use
- History or presence of diabetes
- Any prior ophthalmologic examinations
- History of trauma to the eye
- Any family history of glaucoma, congenital cataracts, or cataracts arising later in life
- Use of corrective lenses (contact lenses or eyeglasses)
- History of prolonged exposure to sunlight or ultraviolet light and use of sunglasses
- History of exposure to secondhand smoke

11.5.7 Contraception and Pregnancy

11.5.7.1 Contraception

The effects of LUM monotherapy or LUM in combination with IVA on the PK of hormonal contraceptives are not known; however, since LUM is a strong inducer of CYP3A, it may reduce the effectiveness of hormonal contraceptives.

Participation in this study requires a commitment from the subject and his/her partner to use at least 1 effective method of birth control as a couple. 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 LUM/IVA (unless otherwise noted) until 90 days following the last dose of LUM/IVA.

Definition of Childbearing Potential

All female subjects who have had their first menstrual period, from the time of the screening assessment through the Safety Follow-up Visit, including subjects with tubal ligations and subjects who do not have a documented hysterectomy, will be considered to be of childbearing potential unless:

- The subject has had a documented hysterectomy or bilateral oophorectomy/ salpingo-oophorectomy
- The subject is postmenopausal, defined as at least 12 months of continuous spontaneous amenorrhea with serum FSH levels ≥40 mIU/L.

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 LUM/IVA.

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 postvasectomy 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 (nonhormone-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(nonhormone-releasing and hormone-releasing intrauterine devices are permitted)
- 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 at the time of screening 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 LUM/IVA, throughout the study, and for 90 days following the last dose of LUM/IVA.
- 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 LUM/IVA.
- Female subjects should not nurse a child from the start of LUM/IVA dosing through 90 days following the last dose of LUM/IVA.

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.

11.5.7.2 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 LUM/IVA.

If a subject or the female partner of a male subject becomes pregnant while participating in the study, LUM/IVA will be permanently discontinued immediately. The investigator will 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 will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

[redacted]

[redacted]

12 STATISTICAL AND ANALYTICAL PLANS

This section presents a summary of the planned statistical analyses for this protocol. Statistical analysis details will be provided in the Statistical Analysis Plan (SAP).

The Vertex Biometrics department or a designated CRO will analyze the data derived from this study. SAS® Version 9.2 or later will be used to generate all statistical outputs (tables, figures, listings, and data sets).

12.1 Sample Size and Power

A total of approximately 75 subjects will be enrolled and will be randomized at 2:1 ratio to 1 of 2 study arms: Study Arm A(approximately 50 subjects) and Study Arm B, (approximately 25 subjects).

The primary endpoint is the mean percentage adherence to LUM/IVA treatment over 48 weeks. Assuming a standard deviation (SD) of 8, a sample size of 50 in Study Arm A and 25 in Study Arm B will have 80% power to detect a difference of 5.6% between the means for the 2 study arms using a 2-sided, 2-sample *t*-test at the 0.05 significance level.

Data from studies VX09-809-102, VX12-809-103, and VX12-809-104 were used for this sample size calculation. Sample sizes based on a range of SDs [redacted].

12.2 Analysis Sets

The Full Analysis Set (FAS) will include all randomized subjects who received at least 1 dose of LUM/IVA. The FAS will be used for all analyses in this study.

The Safety Set will include all subjects who received at least 1 dose of LUM/IVA. The Safety Set will be used for all safety analyses, unless otherwise specified.

12.3 Statistical Analysis

The primary objective of this study is to evaluate the impact of smart adherence technologies on LUM/IVA adherence rates among patients aged 16 years of age and older with CF who are homozygous for the *F508del*. The secondary objective is to collect subject and physician feedback on the use of smart adherence technology. This section presents a summary of the planned statistical analyses to address the endpoints associated with study's objectives.

Statistical analysis and presentation details will be provided in the SAP for the study.

12.3.1 General Considerations

All subject data, including those derived will be presented in subject data listings; listings will display all subjects who were randomized, regardless of whether or not they received LUM/IVA.

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

Categorical data will be summarized using counts and percentages.

Unless specified otherwise, only descriptive analyses will be performed (i.e., no statistical hypothesis testing will be performed).

Baseline for a variable, unless otherwise specified, will be defined as the most recent nonmissing measurement (scheduled or unscheduled) collected at or before Day 1 of the study.

Change from baseline will be calculated as postbaseline value minus baseline value.

Rules for handling missing data will be described in the SAP.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

The number and percentage of subjects in each disposition category (e.g., randomized, included in the FAS, included in the Safety Set, completed study/Safety Follow-up Visit, and discontinued use of smart adherence technology or study with a breakdown of the reasons for discontinuation) will be summarized overall and by study arms.

12.3.2.2 Demographics and Baseline Characteristics

Demographic, background (e.g., medical history), and baseline characteristics will be summarized using descriptive summary statistics.

The following demographics and baseline characteristics will be summarized overall and by study arm for the FAS and will include (but are not limited to): sex, race, age, baseline weight, baseline height, baseline body mass index (BMI), and baseline patient-reported outcomes (PROs).

No statistical tests will be carried out to evaluate any baseline imbalance between study arms.

12.3.2.3 Prior and Concomitant Medications

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

- **Prior medication:** any medication that started before initial dosing of LUM/IVA, regardless of when dosing of the medication ended
- **Concomitant medication:** medication received at or after the first dose of LUM/IVA, medication that was received before initial dosing and continued after initial dosing of LUM/IVA, or medication with missing stop date
- **Post-treatment medication:** medication continued or newly received after the treatment-emergent period. A given medication can be classified as a prior medication, a concomitant medication, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether the medication was taken before the first dose of LUM/IVA, concomitantly, or after the treatment-emergent period, it will be considered as prior, concomitant, and post-treatment.

Prior medications and concomitant medications will be summarized by study arms based on the FAS. Post-treatment medications will be provided separately in an individual subject data listing.

12.3.2.4 Study Drug Exposure and Compliance

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

Primary and secondary analyses of adherence will be performed through smart technology generated data. A complementary analysis based on pill count and missing/interruption of dose

will be conducted. Information on number of pills and drug interruption will be collected from dispensing pharmacy and subjects.

These pharmacy and subject reported compliance data will be summarized for the FAS and will be derived in at least 1 of 2 methods pending data availability:

(1) based on pill counts calculated as:

100 × (total number of tablets taken) / (4 × duration of LUM/IVA exposure in days)

And/or:

(2) based on medication interruption days using the formula:

100 × [1 – (total number of days LUM/IVA interrupted ≥72) / (duration of LUM/IVA exposure)]

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

12.3.3 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that has the potential to affect the interpretation of study results. The rules for identifying an IPD will be described in the SAP.

All IPDs will be provided in an individual subject data listing

12.3.4 Analysis of Endpoints

12.3.4.1 Analysis of Primary Endpoints

The primary endpoint is the mean percentage adherence to LUM/IVA treatment over 48 weeks.

The primary analysis for the primary endpoint will be based on an ANCOVA with mean percentage adherence over 48 weeks as the dependent variable, study arm as a fixed effect with covariates for age (<23 versus ≥23 years old), FEV_1 (<70% versus ≥70% predicted), [redacted] and sex (male versus female), at screening. [redacted]

Summary statistics for each arm of the study will be provided. Given the exploratory nature of this study, no multiplicity adjustment of type I error will be applied for these analyses.

Summary of weekly adherence data will be provided; pattern of adherence over 48 weeks will be plotted and may be modeled using mixed effects models.

12.3.4.2 Analysis of Secondary Endpoints

Mean percentage adherence to LUM/IVA treatment over 24 weeks: Analysis of this variable will be similar to that of the primary analysis of the primary endpoint.

Mean percentage adherence to LUM/IVA treatment from Week 25 through Week 48: Analysis of this variable will be similar to that of the primary analysis of the primary endpoint.

Proportion of subjects with ≥80% LUM/IVA adherence over 24 weeks: This endpoint will be analyzed using a logistic regression model with Study Arm as a fixed effect and covariates for

age (<23 versus ≥23 years old), FEV_1 (<70% versus ≥70% predicted), [redacted] and sex (male versus female), at the screening. In case of model non-convergence and for sensitivity analysis, a 2-sided Cochran-Mantel-Haenszel (CMH) test stratified by the same covariates as in the logistic regression will be provided. The estimate of odds ratio and the corresponding 95% CI will be provided.

Proportion of subjects with ≥80% LUM/IVA adherence over 48 weeks: Analysis of this variable will be similar to that of the proportion of subjects with ≥80% adherence over 24 weeks.

Proportion of subjects with ≥80% LUM/IVA adherence from Week 25 through Week 48: Analysis of this variable will be similar to that of the proportion of subjects with ≥80% adherence over 24 weeks.

Proportion of subjects with a non-physician-directed LUM/IVA interruption ≥72 hours over 48 weeks: Analysis of this endpoint will be similar to that of the proportion of subjects with ≥80% adherence over 24 weeks.

Number of non-physician-directed LUM/IVA interruptions ≥72 hours over 48 weeks: For number of drug interruptions, comparison between the study arms will be carried out using negative binomial regression model with Study Arm as a fixed effect and age group (<23 versus ≥23 years old), FEV_1 (<70% versus ≥70% predicted), [redacted] and sex (male versus female), at the screening as covariates.

The log of time spent in the study will be treated as the offset in this model.

In addition, a stratified Wilcoxon's rank-sum test by adjusting for age group, $ppFEV_1$, [redacted] and sex may be performed as a sensitivity analysis, if needed.

Time to the first non-physician-directed LUM/IVA interruption ≥72 hours over 48 weeks: Time-to-first LUM/IVA interruption ≥72 hours over 48 weeks will be analyzed using Cox regression. A Cox PH regression model will include a main effect of Study Arm and covariates for age (<23 versus ≥23 years old), FEV_1 (<70% versus ≥70% predicted), [redacted] and sex (male versus female), at the screening visit. Additionally, Kaplan-Meier method will be used to produce graphical presentation of the survival curves. Log-rank test and Wilcoxon test will also be summarized.

[redacted]

[redacted]

12.3.5 Safety Analysis

All safety analyses will be based on the set of data associated with the treatment-emergent period for subjects in the Safety Set.

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

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., liver function tests)
- Vital signs
- Ophthalmological examinations

All safety data will be presented in individual subject data listings.

12.3.5.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs, or post-treatment AEs, defined as follows:

- **Pretreatment AE:** any AE that started before the first dose of LUM/IVA
- **TEAE:** any AE that increased in severity or that was newly developed at or after the first dose of LUM/IVA to 28 days after the last dose of LUM/IVA
- **Post-treatment AE:** any AE that increased in severity or that was newly developed after 28 days after the last dose of LUM/IVA

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

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

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

Summaries will be presented by MedDRA System Organ Class and preferred term using frequency counts and percentages by study arm (i.e., number and percentage of subjects with an event as well as total number of events). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once; only the maximum severity level will be presented in the severity summaries and the worst/highest relationship level presented in the relationship summaries. In addition, summary tables containing individual subject AE data for all deaths and other serious and significant AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

AEs leading to death, SAEs, dose interruption, and permanent discontinuation will be listed separately. All AEs through the Safety Follow-up Visit will be listed in an individual subject data listing, including pre-treatment AEs.

12.3.5.2 Clinical Laboratory Assessments

For the on-treatment laboratory measurements, the raw values and change from baseline values of the liver function test results will be summarized in SI units by study arms at each visit. For liver function, the number and percentage of subjects with abnormal low (<LLN) value and with abnormal high (>ULN) value at each scheduled time point will be summarized.

The number and percentage of subjects with at least 1 potentially clinically significant (PCS) event during the treatment-emergent period will be summarized. Clinically significant abnormal laboratory findings will be reported as AEs.

12.3.5.3 Vital Signs

The following vital signs will be summarized by study arms at each scheduled time point: systolic and diastolic blood pressure (mmHg), oral temperature, pulse rate (beats per minute [bpm]), and respiratory rate (breaths per minute). Clinically significant abnormal findings in vital signs will be reported as AEs.

12.3.5.4 Physical Examination

PE results will be presented in individual subject data listings only. Clinically relevant results identified after screening will be reported as AEs.

12.3.5.5 Other Safety Analysis

Not applicable

12.3.6 Interim and IDMC Analyses

12.3.6.1 Interim Analysis

No interim analysis is planned for this study.

12.3.6.2 IDMC Analysis

Not applicable

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

Study assessments including laboratory tests, PEs, and vital signs, will be assessed and those deemed 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 LUM/IVA 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 AEs will be collected from the time the ICF is signed until the following time points:

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, the **earliest** of:
  - 28 days after the last dose of LUM/IVA or
  - Dosing with commercial LUM/IVA

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. AEs for subjects who are screened but not subsequently enrolled in the study will be recorded only in the subject's source documents. The following data will be documented for each AE:

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

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed Month year). AEs of CTCAE Grades 4 and 5 should be documented as "life-threatening." In considering the severity of an AE in a pediatric subject, the investigator should 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 scale should be determined according to the definitions in Table 13-1. Clinically significant laboratory tests should be recorded as AEs in the subject's source documents and eCRF.

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 LUM/IVA. 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 LUM/IVA, a plausible mechanism for the event to be related to the investigational LUM/IVA and causes other than the investigational LUM/IVA have been ruled out, and/or the event re-appeared on re-exposure to the investigational LUM/IVA.
Possibly related	There is an association between the event and the administration of the investigational LUM/IVA and there is a plausible mechanism for the event to be related to investigational LUM/IVA, 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 LUM/IVA and likely to be related to factors other than investigational LUM/IVA.
Not related	The event is related to an etiology other than the investigational LUM/IVA (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 LUM/IVA 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	LUM/IVA dose not changed in response to an AE
Dose reduced	LUM/IVA dose reduced in response to an AE
Drug interrupted	LUM/IVA administration interrupted in response to an AE
Drug withdrawn	LUM/IVA administration permanently discontinued in response to an AE
Not applicable	Action taken regarding LUM/IVA 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 LUM/IVA. 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 LUM/IVA)
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred

- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Congenital anomaly or birth defect
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home)

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

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

13.1.2.2 Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through the Safety Follow-up Visit, regardless of causality, will be reported by the investigator to Vertex GPS. In addition, all SAEs that occur after the Safety Follow-up Visit and are considered related to LUM/IVA 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 LUM/IVA and possible etiologies. On the SAE Form, relationship to LUM/IVA will be assessed only as related (includes possibly related) or not related (includes unlikely related), and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report to Vertex the outcome of the event using the SAE Form.

13.1.2.3 Reporting Serious Adverse Events

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

Please send completed SAE Forms to Vertex GPS via
Email: [redacted] (Preferred Choice)
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 LUM/IVA to all regulatory authorities and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to central independent ethics committees (IECs).

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

13.2 Administrative Requirements

13.2.1 Ethical Considerations

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

13.2.2 Subject Information and Informed Consent

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

13.2.3 Investigator Compliance

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

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all 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/EC, 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.

14 REFERENCES

1 Australian Cystic Fibrosis Data Registry. Cystic fibrosis in Australia 2009: 12th annual report. Baulkham Hills, New South Wales, Australia: Cystic Fibrosis Australia; 2011.

2 FDA Office of Orphan Products Development. Developing Products for Rare Diseases & Conditions. Available at: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm. Accessed 01 July 2015.

3 European Medicines Agency. Committee for Orphan Medicinal Products (COMP). Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000263.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028e30. Accessed 01 July 2015.

4 Cystic Fibrosis Foundation Patient Registry. 2012 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation; 2013.

5 Stern M, Wiedemann B, Wenzlaff P. From registry to quality management: The German Cystic Fibrosis Quality Assessment Project 1995-2006. Eur Respir J. 2008;31(1):29-35.

6 Cystic Fibrosis Trust. Cystic Fibrosis Trust annual review 2010. London, UK: Cystic Fibrosis Trust; 2012.

7 Kriendler JL. Cystic fibrosis: exploiting its genetic basis in the hunt for new therapies. Pharmacol Ther. 2010;125:219-29.

8 Flume PA, Van Devanter DR. State of progress in treating cystic fibrosis respiratory disease. BMC Med. 2012;10(1):88.

9 Cystic Fibrosis Mutation Database (CFTR1). Cystic Fibrosis Centre at the Hospital for Sick Children in Toronto Web Site [Internet]. Available from: http://www.genet.sickkids.on.ca. Assessed 15 February 2016.

10 Wildman, M J. Moving cystic fibrosis care from rescue to prevention by embedding adherence measurement in routine care. Pediatr Respir Rev. 2014;16-18.

11 Payer, JZ. Therapeutic adherence to biophosphonates. Biomed Pharmacother. 2007;191-3.

12 Siracusa C, Ryan J, Burns, L, Wang Y, Zhang N, Clancy J, et al. Electronic monitoring reveals highly variable adherence patterns in patients prescribed ivacaftor. J Cystic Fibrosis.2015;14:621-6

13 Risser J, Jacobson TA, Kripalani S. Development and psychometric evaluation of the Self-efficacy for Appropriate Medication Use Scale (SEAMS) in low-literacy patients with chronic disease. J Nurs Meas. 2007;15:203–19.

14 Reynolds NR, Sun J, Nagaraja HN, Gifford AL, Wu AW, Chesney MA. Optimizing measurement of self-reported adherence with the AIDS clinical trials group adherence questionnaire: A cross protocol analysis. JAIDS. 2007;14:402-9.

15 Chesney MA, Ickovics JR, Chambers DB, Gifford AL, Neidiq J, Zwicki B, et al. Self-reported adherence to anti-retroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee and Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). AIDS Care. 2000; 12:255-266.

16 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26:319-38.

17 Wang X, Dockery DQ, Wypij D, Fay ME, Ferris BG. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol. 1993;15:75-88.

18 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. Am J Respir Crit Care Med. 1999;159:179-87.

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX15-809-114	Version #: 2.0	Version Date 19 Oct 2016
Study Title: A Phase 4, Open-label Treatment, Randomized, Multicenter, 2-arm, Parallel-group, Pilot Study of Adherence to Lumacaftor/Ivacaftor in CF Subjects Homozygous for the F508del-CFTR Mutation		

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

[redacted]

15.2 Investigator Signature Page

Protocol #: VX15-809-114	Version #: 2.0	Version Date 19 Oct 2016
Study Title: A Phase 4, Open-label treatment, Randomized, Multicenter, 2-arm, Parallel-group, Pilot Study of Adherence to Lumacaftor/Ivacaftor in CF Subjects Homozygous for the F508del-CFTR Mutation		

I have read Protocol VX15-809-114, 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