## 1 TITLE PAGE

*VERTEX PHARMACEUTICALS INCORPORATED*

# Clinical Study Protocol

**A Phase 3, 2-part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for *F508del***

**Vertex Study Number: VX16-809-122**

[redacted]

**EudraCT Number: 2017-004794-13**

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# 2 PROTOCOL SYNOPSIS

**Title** A Phase 3, 2-part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for *F508del*

**Brief Title** Safety and Pharmacokinetic Study of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for *F508del*

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

**Objectives**

**Primary Objectives**

**Part A**

To evaluate the PK of lumacaftor (LUM) and ivacaftor (IVA) in subjects 1 to less than 2 years of age with cystic fibrosis (CF), homozygous for *F508del*

**Part B**

To evaluate the safety of LUM/IVA in subjects 1 to less than 2 years of age with CF, homozygous for *F508del*

**Secondary Objectives**

**Part A**

- To evaluate the safety of LUM/IVA in subjects 1 to less than 2 years of age with CF, homozygous for *F508del*
- To evaluate the PK of the metabolites of LUM and IVA in subjects 1 to less than 2 years of age with CF, homozygous for *F508del*

**Part B**

- To evaluate the pharmacodynamics (PD) of LUM/IVA in subjects 1 to less than 2 years of age with CF, homozygous for *F508del*
- To evaluate the PK of LUM and IVA and their respective metabolites in subjects 1 to less than 2 years of age with CF, homozygous for *F508del*

**Endpoints**

**Primary Endpoints**

**Part A**

PK parameters of LUM and IVA

**Part B**

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

**Secondary Endpoints**

**Part A**

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

**Part B**

- Absolute change from baseline in sweat chloride at Week 24
- PK parameters of LUM, IVA, and their respective metabolites

[redacted]

**Number of Subjects**

**Part A**

Approximately 10 subjects are planned for enrollment, including a minimum of 5 subjects 18 to <24 months of age (Cohort 1) and 5 subjects 12 to <18 months of age (Cohort 2). Subjects who participate in Part A may participate in Part B if they meet eligibility criteria; participation in Part A is not required for participation in Part B.

A review of safety, tolerability, and available PK data will be completed after Part A to determine the dose(s) and/or weight bounds to be evaluated in Part B. Additional subjects or treatment cohorts may be enrolled, if data from the initially planned 10 subjects are inadequate to make a determination of the dose(s) to be evaluated in Part B.

**Part B**

Approximately 30 subjects are planned for enrollment, including a minimum of 10 subjects 18 to <24 months of age and 10 subjects 12 to <18 months of age.

**Study Population**

Male and female subjects 1 to <2 years of age on Day 1 with CF, homozygous for *F508del.*

**Investigational Drug**

Active substance: LUM/IVA fixed-dose combination

Activity: CFTR corrector and potentiator ($Cl^-$ secretion)

Strength and route of administration:

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

**Study Duration**

**Part A**

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

**Part B**

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

**Study Design**

**Part A**

Subjects will be enrolled in Part A sequentially in the following cohorts:

- **Cohort 1**: subjects aged 18 to <24 months
- **Cohort 2**: subjects aged 12 to <18 months

Enrollment in Part A will begin with subjects in Cohort 1.

Part A includes the following:

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

Dose Regimens Investigated and Dose Adjustment

- LUM 75 mg/IVA 94 mg every 12 hours (q12h) for subjects weighing 7 to <10 kg at screening
- LUM 100 mg/IVA 125 mg q12h for subjects weighing 10 to <14 kg at screening
- LUM 150 mg/IVA 188 mg q12h for subjects weighing ≥14 kg at screening

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

Preliminary review of Part A data (e.g., from Cohort 1 and/or Cohort 2) and any updated modeling approaches resulting from such data may result in updated dose recommendations, e.g., for Part B. Changes to study drug dose(s) will be communicated to site personnel through a memorandum entitled "Justification for Dose Selection" to ensure clarity and consistency in study conduct.

A review of safety, tolerability, and available PK data will be completed after each Part A Cohort to confirm or adjust the dose(s) and/or weight bounds to be evaluated in Part B. Additional subjects or treatment cohorts may be enrolled, if data from the initially planned 10 subjects are inadequate to make a determination of the dose(s) to be evaluated in Part B.

**Part B**

Part B includes the following:

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

Dose Regimens Investigated and Dose Adjustment:

- LUM 75 mg/IVA 94 mg q12h for subjects weighing 7 to <10 kg at screening
- LUM 100 mg/IVA 125 mg q12h for subjects weighing 10 to <14 kg at screening
- LUM 150 mg/IVA 188 mg q12h for subjects weighing ≥14 kg at screening

Doses are based on the subject's weight at screening. During the Treatment Period, doses will be adjusted upward if the subject's weight is at or above the lower weight bound of the next higher dose at 2 consecutive study visits. However, no downward dose adjustments will be made if a subject's weight decreases.

The doses and weight bounds listed above are those planned for Part B. Depending on the results from Part A, any changes to study drug dose(s) and/or weight bounds will be communicated to site personnel through a memorandum entitled "Justification for Dose Selection" to ensure clarity and consistency in study conduct.

[redacted]

At the Safety Follow-up Visit, subjects who complete LUM/IVA treatment and the visits in the Treatment Period will be offered the opportunity to enroll in an optional open-label Extension Study evaluating LUM/IVA (enrollment will be based on eligibility criteria specified in the Extension Study).

**Assessments**

**Safety**

AEs, clinical laboratory values (serum chemistry and hematology), ECGs, vital signs, pulse oximetry, physical examinations, and ophthalmologic examinations (**Part B only**)

**Pharmacokinetic**

PK parameters of LUM, IVA, and their respective metabolites

**Pharmacodynamic (Part B only)**

Sweat chloride test, [redacted]

**Statistical Analyses**

**Part A**

Approximately 10 subjects are planned for enrollment, including a minimum of 5 subjects 18 to <24 months of age and 5 subjects 12 to <18 months of age. No formal sample size calculations have been performed. The number of subjects in Part A is common in early clinical pharmacology studies in this age group and is considered sufficient to achieve the PK objectives of Part A.

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

**Part B**

Approximately 30 subjects are planned for enrollment, including a minimum of 10 subjects 18 to <24 months of age and 10 subjects 12 to <18 months of age. Assuming a 10% dropout rate, approximately 27 subjects will complete Part B. No formal sample size calculations have been performed. The number of subjects in Part B is deemed adequate to meet the primary safety objective.

Given a total sample size of 27 subjects (completers), there is a 75.0% chance of observing AEs in at least 1 subject if the true incidence rate is 5%, and a 94.2% chance of observing AEs in at least 1 subject if the true incidence rate is 10%.

For primary safety analyses, overall summary statistics will be provided for treatment-emergent adverse events (TEAEs), clinical laboratory assessments (serum chemistry and hematology), ECGs, vital signs, and pulse oximetry.

Details of the analysis will be provided in the Part B statistical analysis plan. Additional interim analyses may take place at any time during the study if deemed necessary by the Vertex team.

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

# 3 SCHEDULE OF ASSESSMENTS

Schedules of Assessments are shown in Table 3-1, Table 3-2, and Table 3-3.

## Table 3-1 Study VX16-809-122: Part A and Part B Screening

| Assessment | Screening Visit<br>Day -28 through Day -1 |
|---|---|
| Informed consent | X |
| Demographics | X |
| Medical history | X |
| Length, weight, and vital signs[a,b] | X |
| Pulse oximetry[b] | X |
| Ophthalmologic examination[c] | X |
| Full physical examination | X |
| Standard 12-lead ECG[d] | X |
| *CFTR* genotype[e] | X |
| Serum chemistry[f] | X |
| Hematology[f] | X |
| [redacted] | |
| Sweat chloride[h] | X |
| [redacted] | |
| Medications review | Continuous from signing of ICF through Safety Follow-up Visit |
| Adverse events | Continuous from signing of ICF through Safety Follow-up Visit |

BMI: body mass index; [redacted] -1; ICF: informed consent form; [redacted]

[a] Length and weight must be measured with the subject in a dry diaper or dry underclothes only (Section 11.6.4). BMI will be derived from this assessment.

[b] The subject should rest for at least 5 minutes, if possible, before having vital signs and pulse oximetry measured (Section 11.6.4).

[c] An ophthalmologic examination will be conducted by a licensed ophthalmologist, preferably a pediatric ophthalmologist (Section 11.6.6). The examination does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the Screening Visit.

[d] A standard 12-lead ECG will be performed (Section 11.6.5). The subject should rest for at least 5 minutes, if possible, before having an ECG performed. The ECG will be performed before any other procedures that may affect heart rate, such as blood draws.

[e] If a genotype test has been performed previously and is documented in the subject's medical record, the subject is not required to be tested for *CFTR* genotype at screening but the subject's eligibility must be approved by the Vertex medical monitor. If a historic genotype result is not available at screening or if the historic genotype result is not approved by the Vertex medical monitor, subjects will be tested for *CFTR* genotype, and the results must be reviewed before the first dose. Note: Newborn screening genotype results are not sufficient for eligibility.

[f] The results must be received and reviewed before the first dose. Refer to Section 11.6.2 for details.

[redacted]

[h] If a historical sweat chloride result (≥60 mmol/L by quantitative pilocarpine iontophoresis) is documented in the subject's medical record, that result alone (and not the Screening Visit result) may be used to determine eligibility. For subjects using a historical sweat chloride value documented in their medical record to determine eligibility, the sweat chloride test at the Screening Visit is still required in Part B. At screening, 2 samples will be collected, 1 sample from each arm (left and right).

[redacted]

## Table 3-2 Study VX16-809-122: Part A Treatment Period and Safety Follow-up Visit

| Event/Assessment[a] | Day 1 | Day 3 (± 1 Day) | Day 8 (± 1 Day) | Day 15 (± 2 Days) | ETT Visit (As Soon As Possible After Last Dose of Study Drug) | Safety Follow-up Visit 10 (± 3) Days After the Last Dose of Study Drug |
|---|---|---|---|---|---|---|
| Clinic visit | X | | X | X | X | X |
| Telephone contact[b] | | X | | | | |
| **Safety Assessments** | | | | | | |
| Length and weight[c] | X | | | X | X | X |
| Vital signs[d] | X[e] | | X | X[e] | X | X |
| Pulse oximetry[d] | X[e] | | X | X[e] | X | X |
| Full physical examination[f] | X | | | X | X | X |
| Abbreviated physical examination | X[g] | | X | | | |
| Standard 12-lead ECG[h] | | | | X | X | X |
| Serum chemistry[i] | X[j] | | | X | X | X |
| Hematology[i] | X[j] | | | X | X | X |
| Observation 4 hours after the first dose | X | | | | | |
| Medications, treatments, and procedures review | Continuous from signing of ICF through Safety Follow-up Visit | | | | | |
| Adverse events | Continuous from signing of ICF through Safety Follow-up Visit | | | | | |
| **PK Assessments** | | | | | | |
| PK sampling | X[k] | | X[l] | X[m] | X | |

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

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

[c] Length and weight must be measured with the subject in a dry diaper or dry underclothes only (Section 11.6.4). BMI will be derived from this assessment.

[d] The subject should rest for at least 5 minutes, if possible, before having vital signs and pulse oximetry measured (Section 11.6.4).

[e] Vital signs and pulse oximetry will be measured predose and at 1 to 2 hours and 4 to 6 hours postdose on Day 1 and Day 15.

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

[g] An abbreviated physical examination will be performed 4 hours (± 30 minutes) postdose on Day 1 (Section 11.6.4).

[h] A standard 12-lead ECG will be performed (Section 11.6.5). The subject should rest for at least 5 minutes, if possible, before having an ECG performed. The ECG will be performed before any other procedures that may affect heart rate, such as blood draws.

[i] Refer to Section 11.6.2 for details.

[j] If the screening blood sample for serum chemistry and hematology is collected ≤9 days before Day 1, then a chemistry/hematology blood sample will not need to be collected on Day 1.

[k] On Day 1, a PK blood sample will be collected at 3 to 4 hours after the morning dose.

[l] On Day 8, PK blood samples will be collected predose (within 60 minutes before the morning dose).

[m] On Day 15, a PK blood samples will be collected predose (within 60 minutes before the morning dose), and 2 hours (± 15 minutes) and 3 to 4 hours after the morning dose.

## Table 3-2 Study VX16-809-122: Part A Treatment Period and Safety Follow-up Visit

| Event/Assessment[a] | Day 1 | Day 3 (± 1 Day) | Day 8 (± 1 Day) | Day 15 (± 2 Days) | ETT Visit (As Soon As Possible After Last Dose of Study Drug) | Safety Follow-up Visit 10 (± 3) Days After the Last Dose of Study Drug |
|---|---|---|---|---|---|---|
| **Study Drug Administration** | | | | | | |
| LUM/IVA dosing (dose based on weight at screening)[n] | **LUM/IVA q12h** | | | | | |
| Study drug count | | | X | X | X | |

AE: adverse event; BMI: body mass index; CF: cystic fibrosis; ETT: Early Termination of Treatment; ICF: informed consent form; IVA: ivacaftor; LUM: lumacaftor; PK: pharmacokinetic; q12h: every 12 hours

[n] LUM/IVA will be administered q12h (± 1 hour), approximately 30 minutes from the start of consuming fat containing food such as a standard "CF" high-fat, high-calorie meal or snack according to the guidelines in Section 9.6.1. The date, amount taken, time of LUM/IVA administration, including whether food was taken with each dose, and occurrence and time of regurgitation within 1 hour after dosing will be recorded for each dose. The morning dose on Day 15 is the last dose.

## Table 3-3 Study VX16-809-122: Part B Treatment Period and Safety Follow-up Visit

| Event/Assessment[a] | Treatment Period | | | | | | | | | ETT Visit[b] | Safety Follow-up Visit (Week 26 [2 weeks ± 4 days After Last Dose])[c,d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day 1 | Day 3 (± 1 day) | Day 15 (± 3 days) | Week 4 (± 5 days) | Week 8 (± 5 days) | Week 12 (± 5 days) | Week 16 (± 5 days) | Week 20 (± 5 days) | Week 24 (± 5 days) | | |
| Clinic visit | X | | X | X | X | X | X | | X | X | X |
| Telephone contact[e] | | X | | | | | | X | | | |
| Length and weight[f] | X | | X | X | X | X | X | | X | X | X |
| Vital signs[g] | X[h] | | X[h] | X | X | X | X | | X | X | X |
| Pulse oximetry[g] | X[h] | | X[h] | X | X | X | X | | X | X | X |
| Ophthalmologic examination | | | | | | | | | X[i] | X[i] | X[i] |
| Full physical examination[j] | X | | | | | X | | | X | X | X |
| Abbreviated physical examination | X[k] | | X | X | X | | X | | | | |
| Standard 12-lead ECG[l] | | | | X | | X | | | X | X | X |
| Serum chemistry[m] | X[n] | | X (LFTs only) | X | X (LFTs only) | X | X (LFTs only) | | X | X | X |
| Hematology[m] | X[n] | | | X | | X | | | X | X | X |

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

[b] Subjects who prematurely discontinue LUM/IVA treatment will be asked to complete the ETT Visit as soon as possible after their last dose. If the ETT Visit occurs ≥10 days after the last dose of LUM/IVA, then the ETT Visit will replace the Safety Follow-up Visit (i.e., the assessments performed will be those specified for the ETT Visit), and a Safety Follow-up Visit will not be required. Subjects who become eligible to receive commercially available LUM/IVA by prescription of a physician, and who choose to continue onto commercially available LUM/IVA before completion of Part B, must remain on study-supplied LUM/IVA through the ETT Visit and may only initiate treatment with commercially available LUM/IVA after completion of this visit.

[c] The Safety Follow-up Visit is not required for (1) subjects who permanently discontinue LUM/IVA treatment before or at the Week 16 Visit if they return for the Week 24 Visit; (2) subjects who continue onto commercially available LUM/IVA by prescription of a physician within 2 weeks (± 4 days) of completing treatment at Week 24 or at the ETT Visit; or (3) subjects who complete their ETT Visit ≥10 days after the last dose of LUM/IVA.

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

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

[f] Length and weight must be measured with the subject in a dry diaper or dry underclothes only (Section 11.6.4). BMI will be derived from this assessment.

[g] The subject should rest for at least 5 minutes, if possible, before having vital signs and pulse oximetry measured (Section 11.6.4).

[h] Vital signs and pulse oximetry will be measured predose and at 1 to 2 hours and 4 to 6 hours postdose on Day 1 and Day 15.

[i] An ophthalmologic examination will be conducted by a licensed ophthalmologist (preferably a pediatric ophthalmologist) (Section 11.6.6). The examination may be conducted anytime within 12 days of the Week 24 Visit (or ETT Visit, if applicable) through 18 days after the last dose.

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

[k] An abbreviated physical examination will be performed 4 hours (± 30 minutes) postdose on Day 1 (Section 11.6.4).

[l] A standard 12-lead ECG will be performed (Section 11.6.5). The subject should rest for at least 5 minutes, if possible, before having an ECG performed. The ECG will be performed before any other procedures that may affect heart rate, such as blood draws.

[m] Refer to Section 11.6.2 for details.

[n] If the screening blood sample for serum chemistry and hematology is collected ≤9 days before Day 1, then a chemistry/hematology blood sample will not need to be collected on Day 1.

**Table 3-3 Study VX16-809-122: Part B Treatment Period and Safety Follow-up Visit**

| Event/Assessment[a] | Treatment Period: Day 1 | Day 3 (± 1 day) | Day 15 (± 3 days) | Week 4 (± 5 days) | Week 8 (± 5 days) | Week 12 (± 5 days) | Week 16 (± 5 days) | Week 20 (± 5 days) | Week 24 (± 5 days) | ETT Visit[b] | Safety Follow-up Visit (Week 26 [2 weeks ± 4 days After Last Dose])[c,d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PK sampling[o,p] | | | X | X[q] | | X | | | X | X | |
| [redacted] | | | | | | | | | | | |
| Sweat chloride[t] | X[u] | | | X | | X | | | X | X | X |
| [redacted] | | | | | | | | | | | |
| LUM/IVA dosing (dose based on weight at screening)[p,y] | LUM/IVA q12h | | | | | | | | | | |
| Observation 4 hours after the first dose | X | | | | | | | | | | |
| [redacted] | | | | | | | | | | | |
| Study drug count | | | X | X | X | X | X | | X | X | |
| Medications, treatments, and procedures review | Continuous from signing of ICF through Safety Follow-up Visit (if required) | | | | | | | | | | |
| Adverse events | Continuous from signing of ICF through Safety Follow-up Visit (if required) | | | | | | | | | | |

AE: adverse event; [redacted] CF: cystic fibrosis; ETT: Early Termination of Treatment; [redacted]; ICF: informed consent form; [redacted] IVA: ivacaftor; LFT: liver function testing; [redacted] LUM: lumacaftor; [redacted] PK: pharmacokinetic; q12h: every 12 hours

o At the Day 15 and Week 4 Visits, PK blood samples will be collected predose (within 60 minutes before dosing) and 2 to 6 hours postdose. At the Week 12 Visit, PK blood samples will be collected predose (within 60 minutes before dosing). At the Week 24 Visit or the ETT Visit (if applicable), PK blood samples will be collected at the same time as other blood collections.

p The date, amount taken, time of LUM/IVA administration, including whether food was taken with each dose, and occurrence and time of regurgitation within 1 hour after dosing, will be recorded for 1 day (i.e., 2 doses) before PK sample collection and on the days of PK sample collection.

[redacted]

t At each time point, 2 samples will be collected, 1 sample from each arm (left and right).

u The sweat chloride test on Day 1 is not required for subjects who were able to produce a valid sweat sample at screening.

[redacted]

y LUM/IVA will be administered q12h (± 2 hours) within 30 minutes of consuming fat-containing food such as a standard CF high-fat, high-calorie meal or snack according to the guidelines in Section 9.6.2. At the Week 24 Visit, the dose will NOT be administered. The last dose in Part B will be the previous dose administered before the Week 24 Visit.

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## List of Abbreviations

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BMI | body mass index |
| CF | cystic fibrosis |
| *CFTR* | CF transmembrane conductance regulator gene |
| CFTR | CF transmembrane conductance regulator protein |
| CI | confidence interval |
| $Cl^-$ | chloride ion |
| CPAP | clinical pharmacology analysis plan |
| CRF | case report form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | cytochrome P450 |
| ECG | electrocardiogram |
| EDC | electronic data capture |
| EENT | eyes, ears, nose, and throat |
| eGFR | estimated glomerular filtration rate |
| ETT | Early Termination of Treatment |
| *F508del* | *CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein |
| F508del | CFTR protein lacking the phenylalanine normally found at position 508 of the wild-type protein |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| [redacted] | [redacted] |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GPS | Global Patient Safety |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | informed consent form |
| ICH | International Conference on Harmonization |
| IDMC | independent data monitoring committee |
| IEC | independent ethics committee |
| IRB | institutional review board |
| [redacted] | [redacted] |
| IV | intravenous |
| IVA | ivacaftor |
| [redacted] | [redacted] |
| LFT | liver function test |
| LLN | lower limit of normal |
| LUM | lumacaftor |

| Abbreviation | Definition |
|---|---|
| [redacted] | [redacted] |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PD | pharmacodynamics(s) |
| PE | physical examination |
| PK | pharmacokinetic(s) |
| $ppFEV_1$ | percent predicted forced expiratory volume in 1 second |
| PT | Preferred Term |
| q12h | every 12 hours |
| QRS | the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization |
| QT | QT interval |
| QTc | QT interval corrected |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SE | standard error |
| SI | SI units (International System of Units) |
| SOC | System Organ Class |
| SUSAR | suspected, unexpected, serious adverse reaction |
| TE | treatment-emergent |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| US | United States |
| WHODD | World Health Organization Drug Dictionary |

## Glossary of Terms

**Abbreviated study numbers:** In the body of the text, study numbers are abbreviated to the last 3 digits for lumacaftor studies (e.g., Study VX15-809-115 is Study 115).

# 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 more than 70,000 individuals worldwide.[1] Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is approximately 40 years.[2, 3] Although the disease affects multiple organs, progressive loss of lung function is the leading cause of mortality.[4]

CF is caused by a variant in the gene encoding CFTR, an epithelial $Cl^-$ ion channel that is responsible for aiding in the regulation of salt and water absorption and secretion in various tissues.[5] This function is abnormal in patients with CF due to a loss of cell surface expression and/or function of CFTR.

Lumacaftor (LUM; VX-809)/ivacaftor (IVA; VX-770) combination therapy (Orkambi™) is the first medicine designed to treat the underlying molecular defect and enhance the function of CFTR in patients homozygous for *F508del*. The LUM/IVA development program is designed to support the hypothesis that an oral chronic treatment restoring CFTR function can lead to improved pulmonary and extrapulmonary manifestations of CF, prevent progressive lung damage, and ultimately prolong survival.

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

## 5.2 Study Rationale

Approximately half of the total CF patient population is <18 years of age.[2, 6-8] Even before the widespread adoption of newborn screening, the majority of patients with CF were diagnosed in infancy or early childhood due to manifestations of the disease. Pancreatic destruction leading to pancreatic exocrine insufficiency begins in utero, and lung involvement is manifest by pulmonary inflammation and infection that begins shortly after birth.[9, 10]

The primary objectives of the present study are to obtain pharmacokinetic (PK) and safety information to support a proposed indication expansion of LUM/IVA in subjects 1 to <2 years of age with CF, homozygous for *F508del*.

# 6 STUDY OBJECTIVES

## 6.1 Primary Objectives

**Part A**

To evaluate the PK of LUM/IVA in subjects 1 to less than 2 years of age with CF, homozygous for *F508del*

**Part B**

To evaluate the safety of LUM/IVA in subjects 1 to less than 2 years of age with CF, homozygous for *F508del*

## 6.2 Secondary Objectives

**Part A**

- To evaluate the safety of LUM/IVA in subjects 1 to less than 2 years of age with CF, homozygous for *F508del*
- To evaluate the PK of the metabolites of LUM and IVA in subjects 1 to less than 2 years of age with CF, homozygous for *F508del*

**Part B**

- To evaluate the pharmacodynamics (PD) of LUM/IVA in subjects 1 to less than 2 years of age with CF, homozygous for *F508del*
- To evaluate the PK of LUM and IVA and their respective metabolites in subjects 1 to less than 2 years of age with CF, homozygous for *F508del*

# 7 STUDY ENDPOINTS

## 7.1 Primary Endpoints

**Part A**

PK parameters of LUM and IVA

**Part B**

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

## 7.2 Secondary Endpoints

**Part A**

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

**Part B**

- Absolute change from baseline in sweat chloride at Week 24
- PK parameters of LUM, IVA, and their respective metabolites

[redacted]

[redacted]

# 8 STUDY POPULATION

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

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

## 8.1 Inclusion Criteria

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

1. Subject's legally appointed and authorized representative (e.g., parent or legal guardian) will sign and date an informed consent form (ICF).
2. Subject's legally appointed and authorized representative (e.g., parent or legal guardian) is willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, and other study procedures.
3. Subjects (male and female) will be 1 to less than 2 years of age on Day 1 of the relevant part of the study.
4. Weight at the Screening Visit must be within the weight limits as defined for the study drug dose levels (see Table 9-4 and Table 9-5) or according to the dosing guidelines identified in the "Justification for Dose Selection" memorandum effective at the time a subject is screened.

5. Subjects with confirmed diagnosis of CF[11] at the Screening Visit. CF is defined as:
   - 2 CF-causing mutations (all as documented in the subject's medical record)
     - Subjects must be homozygous for *F508del* (genotype to be confirmed at the Screening Visit): If a genotype test has been performed previously and is documented in the subject's medical record, the subject is not required to be tested for *CFTR* genotype at screening, but the subject's eligibility must be approved by the Vertex medical monitor. If a historic genotype result is not available at the Screening Visit or if the historic genotype result is not approved by the Vertex medical monitor, the subject will be tested for *CFTR* genotype at the Screening Visit, and the results must be reviewed before the first dose. Note: Newborn screening genotype results are not sufficient for eligibility.

   AND (1 of the 2 criteria below)

   - chronic sinopulmonary disease OR gastrointestinal/nutritional abnormalities

     OR

   - a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis as documented in the subject's medical record OR from the sweat chloride test result obtained at the Screening Visit. If an eligible historical sweat chloride result is documented in the subject's medical record, that result alone (and not the Screening Visit result) may be used to determine eligibility.
6. Subjects with stable CF disease as deemed by the investigator at the Screening Visit.
7. Subject's legally appointed and authorized representative (e.g., parent or legal guardian) are willing to have the subject remain on a stable CF medication regimen through the Safety Follow-up Visit.

## 8.2 Exclusion Criteria

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

1. History of any comorbidity reviewed at the Screening Visit that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering LUM/IVA to the subject. For example, a history of cirrhosis with portal hypertension.
2. Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject (as deemed by the investigator).
3. Any of the following abnormal laboratory values at the Screening Visit:
   - Hemoglobin <9.5 g/dL
   - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin >2 × upper limit of normal (ULN)
   - Chronic kidney disease of Stage 3 (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 $m^2$ calculated by the Bedside Schwartz equation[12]) based on the normal range for eGFR in this age group (62 to 191 mL/min/1.73 $m^2$)

4. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of LUM/IVA).
5. A standard 12-lead ECG demonstrating QTc >450 msec at the Screening Visit. If QTc exceeds 450 msec at the Screening Visit, the ECG should be repeated 2 more times during the Screening Period, and the average of the 3 QTc values should be used to determine the subject's eligibility.
6. History of solid organ or hematological transplantation.
7. Ongoing or prior participation in an investigational drug study (including studies investigating LUM and/or IVA) within 30 days of the Screening Visit.
   - A washout period of 5 terminal half-lives of the previous investigational study drug, or 30 days, whichever is longer, must elapse before the Screening Visit.
   - The duration of the elapsed time may be longer if required by local regulations.

   Note: Ongoing participation in a noninterventional study (including observational studies) is permitted.
8. Use of restricted medication or food within specified duration before the first dose of LUM/IVA as defined in Section 9.4.
9. An adequate slit-lamp examination could not be conducted at the Screening Visit ophthalmologic examination.
10. History of cataract/lens opacity or evidence of cataract/lens opacity determined to be clinically significant by a licensed ophthalmologist during the ophthalmologic examination at the Screening Visit. The Screening Visit ophthalmologic examination does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the Screening Visit (Section 11.6.6).
11. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study.

# 9 STUDY IMPLEMENTATION

## 9.1 Study Design

### 9.1.1 Overview of Study Design

This is a Phase 3, 2-part, open-label, multicenter study evaluating the PK, safety, and PD of multiple doses of LUM/IVA in subjects 1 to <2 years of age with CF, homozygous for *F508del*. Subjects who participate in Part A may participate in Part B if they meet eligibility criteria.

#### 9.1.1.1 Part A

Figure 9-1 depicts the schematic for the Part A study design.

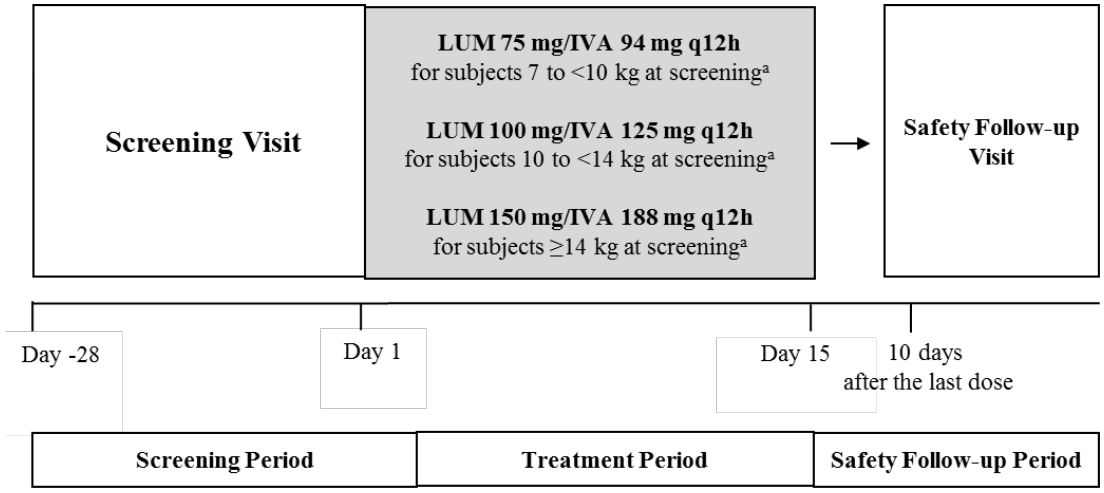
Subjects will be enrolled in Part A sequentially in the following cohorts:

- **Cohort 1**: subjects aged 18 to <24 months
- **Cohort 2**: subjects aged 12 to <18 months

Enrollment in Part A will begin with subjects in Cohort 1.

A review of safety, tolerability, and available PK data will be completed after each Part A Cohort (e.g., Cohort 1 and Cohort 2) to confirm or adjust the dose(s) and/or weight bounds to be evaluated in Part B. Additional subjects or treatment cohorts may be enrolled, if data from the initially planned 10 subjects are inadequate to make a determination of the dose(s) to be evaluated in Part B.

**Figure 9-1 Schematic of Study Design for Part A (Cohort 1 and Cohort 2)**




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

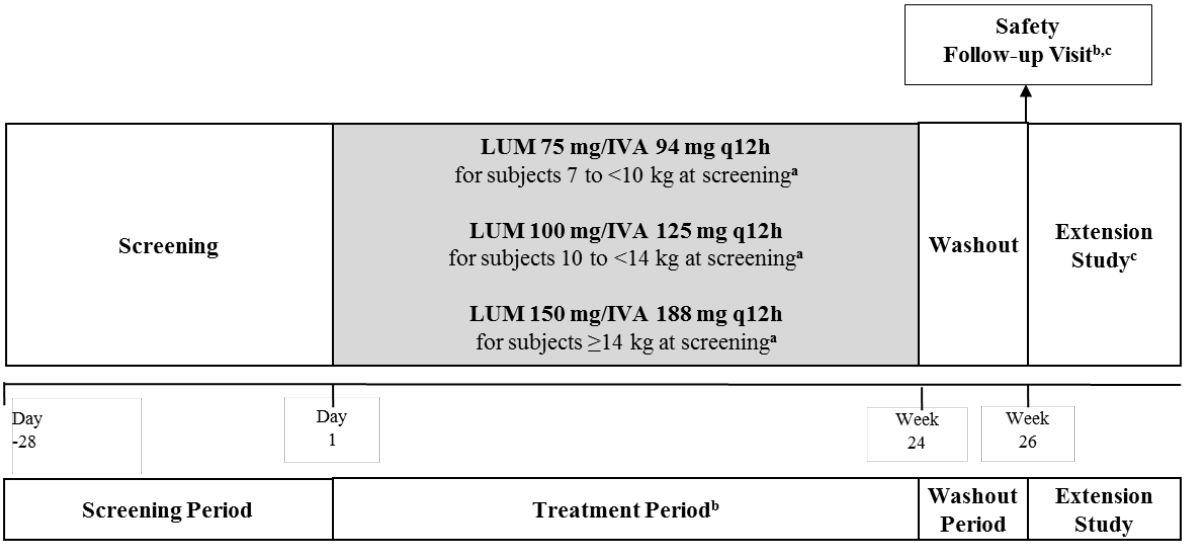
Notes: Approximately 10 subjects are planned for enrollment, including a minimum of 5 subjects 18 to <24 months of age (Cohort 1) and 5 subjects 12 to <18 months of age (Cohort 2).

[a] Doses are based on the subject's weight at screening in Part A. No dose adjustments will be made across the duration of treatment. On Day 15, only the morning dose will be administered. Refer to Section 9.6.1 for additional study drug administration details.

#### 9.1.1.2 Part B

Figure 9-2 depicts the schematic for the Part B study design. [redacted]

**Figure 9-2 Schematic of Study Design for Part B**




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

Notes: Approximately 30 subjects are planned for enrollment, including a minimum of 10 subjects 18 to <24 months of age and 10 subjects 12 to <18 months of age.

[a] The doses and weight bounds listed above are those planned for Part B. Doses are based on the subject's weight at screening in Part B. During the Treatment Period, doses will be adjusted upward if the subject's weight is at or above the lower weight bound of the next higher dose at 2 consecutive study visits. However, no downward dose adjustments will be made if a subject's weight decreases. Refer to Section 9.6.2 for additional study drug administration details. The last dose of LUM/IVA in Part B will be the evening dose before the Week 24 Visit.

[b] Refer to Sections 9.1.3.2, 9.1.5.2, and 9.6.2 for details.

[c] At the Safety Follow-up Visit, subjects who complete LUM/IVA treatment and the visits in the Treatment Period will be offered the opportunity to enroll in an optional open label Extension Study evaluating LUM/IVA (enrollment will be based on eligibility criteria specified in the Extension Study). The Safety Follow-up Visit, if applicable, is the last visit for Part B, and should also be the Day 1 Visit in the Extension Study.

### 9.1.2 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 from the subject's parent or legal guardian.

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

#### 9.1.2.1 Repetition of Screening Assessments

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

- If there is clear evidence of a laboratory error (e.g., hemolyzed sample), equipment malfunction, or technician error, collection of a repeat sample for the appropriate laboratory test may be permitted after discussion with the Vertex medical monitor or authorized designee.
- Exclusionary liver function test (LFT) levels, which may be retested within 14 days of the original Screening Visit date.
- If an adequate slit-lamp examination could not be conducted (Section 11.6.6).
- If QTc exceeds 450 msec at the Screening Visit (see Section 8.2, exclusion criterion 5), the ECG should be repeated 2 more times during the Screening Period, and the average of the 3 QTc values should be used to determine the subject's eligibility.

If repeat values of the individual assessment(s) are within the eligibility criteria and completed within the Screening Period window or extended screening window (Section 9.1.2.3), then the subject is eligible for the study.

#### 9.1.2.2 Rescreening

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

#### 9.1.2.3 Extension of Screening Period Window

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

- Repetition of the Screening Period assessments (Section 9.1.2.1)
- Unexpected operational or logistical delays (e.g., delayed drug shipment)
- To account for exclusionary events that may not reflect the subject's true baseline due to an acute event, which may resolve
- Scheduling of the ophthalmologic examination (Section 11.6.6)
- Availability or malfunction of required equipment or technician error

The screening window can be extended by 4 weeks if a slit-lamp examination must be repeated (Section 9.1.2.1 and Section 11.6.6).

### 9.1.3 Treatment Period

#### 9.1.3.1 Part A

Treatment Period assessments are listed in Table 3-2. Subjects will be outpatients during the Treatment Period. All visits should occur within the windows specified.

The Treatment Period is 15 days; LUM/IVA will be administered every 12 hours (q12h) from Day 1 through Day 15. The morning LUM/IVA dose on Day 15 will be the last dose. LUM/IVA administration and management details are provided in Section 9.6.1 and Section 10.

Procedures for subjects who prematurely discontinue LUM/IVA treatment are described in Section 9.1.6.1.

#### 9.1.3.2 Part B

Treatment Period assessments are listed in Table 3-3. Subjects will be outpatients during the Treatment Period. All visits should occur within the windows specified.

The Treatment Period is 24 weeks; LUM/IVA will be administered q12h from Day 1 through Week 24. The evening LUM/IVA dose before the Week 24 Visit will be the last dose in Part B. LUM/IVA administration and management details are provided in Section 9.6.2 and Section 10.

Procedures for subjects who prematurely discontinue LUM/IVA treatment are described in Section 9.1.6.2.

### 9.1.4 Washout Period

#### 9.1.4.1 Part A

Not applicable

#### 9.1.4.2 Part B

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

### 9.1.5 Follow-up

#### 9.1.5.1 Part A

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

#### 9.1.5.2 Part B

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

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

The Safety Follow-up Visit is not required for the following:

- Subjects who permanently discontinue LUM/IVA treatment before or at the Week 16 Visit if they return for the Week 24 Visit

- Subjects who continue onto commercially available LUM/IVA by prescription of a physician within 2 weeks (± 4 days) of completing LUM/IVA treatment at Week 24 or at the Early Termination of Treatment (ETT) Visit
- Subjects who complete their ETT Visit ≥10 days after the last dose of LUM/IVA (Section 9.1.6.2)

### 9.1.6 Early Discontinuation/Early Termination of Treatment

#### 9.1.6.1 Part A

Subjects who permanently discontinue LUM/IVA treatment for any reason (except withdrawal of consent) will be asked to return to the study site as soon as possible after their last dose of LUM/IVA to complete the ETT Visit. The assessments to be completed are shown in Table 3-2. Additional safety assessments may also be performed at the discretion of the investigator, including possible consultation with a specialist consultant. The Vertex medical monitor will be informed about these additional assessments, and any additional data collected (e.g., as the result of an outside consultation) will be considered part of the study record to provide the most complete safety profile of the study drug.

#### 9.1.6.2 Part B

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

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

### 9.1.7 Independent Data Monitoring Committee

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

## 9.2 Method of Assigning Subjects to Treatment Groups

This is an open-label study with weight-based treatment. Randomization is not required.

## 9.3 Rationale for Study Design and Study Drug Regimens

### 9.3.1 Study Design

This is a Phase 3, 2-part, open-label, multicenter study evaluating the PK, safety, and PD of multiple doses of LUM/IVA in subjects 1 to <2 years of age with CF, homozygous for *F508del*.

Part A will evaluate the PK and safety of LUM/IVA over 15 days of dosing. The evaluation of LUM/IVA as multiple doses allows for the assessment of the time-dependent induction effect of LUM on the metabolism of IVA. The duration of dosing in Part A was selected to evaluate the PK and safety endpoints when the induction effect of LUM on the metabolism of IVA was anticipated to have reached steady state. Part B is designed to evaluate the safety of LUM/IVA dosing over 24 weeks in this pediatric CF population. In addition, the PD effects and PK of multiple doses of LUM/IVA over 24 weeks of dosing will be evaluated, and a 2-week Washout Period is included in order to evaluate the off-drug PD response in this open-label study.

Vertex has established efficacy, safety, and PK profiles for LUM/IVA in subjects 6 years of age and older with CF, homozygous for *F508del* (Studies 103, 104, and 109). Because the underlying genetic and molecular etiology of the disease is identical between younger and older patients, and the outcome of therapy is likely to be comparable, extrapolation of efficacy from older to younger patients is appropriate, and PK studies in younger patients, together with safety studies, can provide adequate information for use.[13]

Safety and PK profiles for LUM/IVA have been established in subjects 2 through 5 years of age with CF, homozygous for *F508del* (Study 115). The present study is designed to obtain PK and safety information to support a proposed indication expansion of LUM/IVA in subjects 1 to <2 years of age with CF, homozygous for *F508del*. The open-label design is considered adequate to evaluate the PK and safety of LUM/IVA in this pediatric population.

### 9.3.2 Study Drug Dose and Duration

**Rationale for Dose**

Part A of this study is designed to characterize the safety and PK of LUM and IVA in subjects 1 to <2 years of age. The plasma concentration versus time data from Part A is intended to inform the appropriateness or necessary adjustment of planned doses for Part B. A population PK model with maturation function and allometric scaling of clearance and volume of distribution as a function of weight was used to project exposures of LUM and IVA for comparison with clinical experiences with both study drugs and to select doses to be evaluated in this study population. The IVA model was coupled to the LUM model to account for the induction of CYP3A by LUM, which increases the metabolism of IVA. Thus, the IVA clearance is impacted by the weight dependence for the clearance of IVA alone and LUM exposure-dependent induction effect. The population PK model is based on data obtained from subjects 2 years of age and older across the LUM and IVA combination development program.

In the combination program, the dose regimen of LUM 400 mg/IVA 250 mg q12h was used in the Phase 3 studies (Studies 103 and 104) for subjects 12 years of age and older. In Phase 3 Studies 109 and 011, the dose regimen of LUM 200 mg/IVA 250 mg q12h was used for subjects 6 through 11 years of age. In Phase 3 Study 115, the dose regimen of LUM 100 mg/IVA 125 mg q12h (body weight <14 kg) or LUM 150 mg/IVA 188 mg q12h (body weight ≥14 kg) was used for subjects 2 through 5 years of age. The LUM and IVA exposures from these studies are summarized in Table 9-1. Based on the initial simulations for subjects 1 to <2 years of age,

the LUM doses selected for Part A are expected to yield exposures that are comparable to those of subjects 2 years of age and older, in whom LUM/IVA combination therapy has been shown to be safe and well tolerated.

IVA as a single agent was previously investigated and approved for use in pediatric patients with CF, 2 to <6 years of age with select mutations. In the Phase 3 study for this population, pediatric subjects who weighed <14 kg received oral administration of IVA granules, 50 mg q12h, and had a mean $AUC_{ss}$ of 10.5 µg·h/mL; pediatric subjects 2 to <6 years of age who weighed ≥14 kg received IVA granules, 75 mg q12h, and had a mean $AUC_{ss}$ of 11.3 µg·h/mL. In the combination program, due to the induction effect of LUM on the metabolism of IVA, the IVA exposures are lower than that of IVA monotherapy. The IVA $AUC_{ss}$ for subjects 2 years of age and older in the combination program are summarized in Table 9-1. Based on the initial simulations for subjects 1 to <2 years of age, the IVA doses selected for Part A are expected to yield IVA exposures that are comparable to subjects 6 years of age and older and within prior clinical experience with IVA alone and IVA given in combination with LUM.

**Table 9-1 Summary of LUM and IVA Exposures in Subjects With CF Who Are 2 Years of Age and Older**

| | LUM $AUC_{0\text{-}12h}$ (µg·h/mL) | IVA $AUC_{0\text{-}12h}$ (µg·h/mL) |
|---|---|---|
| **Age Group** | **Mean (SD)** | **Mean (SD)** |
| 2 through 5 years (weight <14 kg) | 180 (45.5) | 5.92 (4.61) |
| 2 through 5 years (weight ≥14 kg) | 217 (48.6) | 5.90 (1.93) |
| 6 through 11 years (pediatrics) | 224 (59.1) | 6.17 (2.68) |
| 12 through 17 years (adolescents) | 241 (61.4) | 3.89 (1.56) |
| 18 years and older (adults) | 217 (47.9) | 3.80 (1.94) |

Source: Report N329 (Tables 7-4 and 7-7)[14]
CF: cystic fibrosis; IVA: ivacaftor; LUM: lumacaftor; PK: pharmacokinetic; q12h: every 12 hours
Notes: PK data are from Study 115 (2 through 5 years of age), Studies 011 Part B and 109 (6 through 11 years of age), and Studies 103 and 104 (12 through 17 years of age; 18 years of age and older). Subjects in Study 115 received LUM 100 mg/IVA 125 mg q12h (body weight <14 kg) or LUM 150 mg/IVA 188 mg q12h (body weight ≥14 kg) for 24 weeks, subjects in Studies 011 and 109 received LUM 200 mg/IVA 250 mg q12h for 24 weeks, and subjects in Studies 103 and 104 received LUM 400 mg/IVA 250 mg q12h for 24 weeks.

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

Preliminary data and any updated modeling approaches resulting from such data may result in updated dose recommendations. Changes to study drug dose(s) will be communicated to site personnel through a memorandum entitled “Justification for Dose Selection” to ensure clarity and consistency in study conduct.

The population PK models for LUM and IVA were updated with the PK data from Part A Cohort 1 (subjects 18 to <24 months of age). The following adjustments to the originally planned

dose and weight bounds were made so that the simulated exposures for subjects 1 to <2 years of age match the adult range of exposures that showed clinical benefit:

- The lower weight bound for the 100 mg LUM/125 mg IVA q12h dose in Part B was adjusted from 8 kg to 10 kg, such that subjects weighing 10 to <14 kg at screening would receive this dose in Part B
- A lower dose of 75 mg LUM/94 mg IVA q12h was developed for subjects weighing 7 to <10 kg at screening

**Rationale for the Duration of Dosing**

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

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

### 9.3.3 Rationale for Study Assessments

The safety and PK assessments are standard parameters for clinical studies in drug development and are generally recognized as reliable, accurate, and relevant to the study of subjects with CF. Ophthalmologic examinations were added as part of safety monitoring. Assessments were added to evaluate the PD effects of LUM/IVA. The following PD assessments are standard assessments used in studies in the LUM/IVA development program: [redacted] sweat chloride, [redacted] Rationale is provided below for ophthalmologic examinations. [redacted]

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

[redacted]

## 9.4 Study Restrictions

Prohibited medications and certain foods are not allowed as summarized in Table 9-2 (**Part A**) and Table 9-3 (**Part B**).

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

**Table 9-2 Study Restrictions: Part A**

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

IVA: ivacaftor; LUM: lumacaftor; PK: pharmacokinetics
Note: The use of restricted medication in subjects with a medical need will be addressed on a case-by-case basis with the medical monitor or authorized designee.

**Table 9-3 Study Restrictions: Part B**

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

IVA: ivacaftor; LUM: lumacaftor
Note: The use of restricted medication in subjects with a medical need will be addressed on a case-by-case basis with the medical monitor or authorized designee.

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

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

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

## 9.5 Prior and Concomitant Medications

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

- It is recommended that subjects remain on a stable medication regimen for their CF from 28 days before Day 1 through the Safety Follow-up Visit, if applicable. Stable medication

regimen is defined as the current medication regimen for CF that subjects have been following for at least 28 days before Day 1.

- While the etiology of respiratory events associated with LUM/IVA is not yet known, data from healthy subjects in Study 009 Cohort 4 suggest that treatment with short-acting bronchodilators may reverse the initial transient decline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) when dosed with LUM/IVA. Subjects may be prescribed a short-acting bronchodilator in accordance with local drug labeling (if not already prescribed) to ensure constant availability during the study.
- Information about bronchodilator use during the study will be collected and documented in the subject's source documents.

[redacted]

## 9.6 Administration

### 9.6.1 Part A

LUM/IVA will be administered orally as shown in Table 9-4.

**Table 9-4 Study Drug Administration: Part A**

| Dose[a] | Time | LUM/IVA (Number of stick packs) |
|---|---|---|
| **Subject screening weight 7 to <10 kg[a,b]** LUM 75 mg/IVA 94 mg q12h | AM | 1 stick pack |
| | PM | 1 stick pack |
| **Subject screening weight 10 to <14 kg[a,b]** LUM 100 mg/IVA 125 mg q12h | AM | 1 stick pack |
| | PM | 1 stick pack |
| **Subject screening weight ≥14 kg[a,b]** LUM 150 mg/IVA 188 mg q12h | AM | 1 stick pack |
| | PM | 1 stick pack |

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

[a] Preliminary review of Part A data (e.g., from Cohort 1 and/or Cohort 2) and any updated modeling approaches resulting from such data may result in updated dose recommendations, e.g., for Part B. Changes to study drug dose(s) will be communicated to site personnel through a memorandum entitled "Justification for Dose Selection" to ensure clarity and consistency in study conduct.

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

LUM/IVA will be administered approximately 30 minutes from the start of consuming fat-containing food such as a standard "CF" high-fat, high-calorie meal or snack according to the following guidelines:

1. The morning LUM/IVA dose will be administered at the study site on Days 1, 8, and 15.
2. The date, amount taken, time of LUM/IVA administration, including whether food was taken with each dose, and occurrence and time of regurgitation within 1 hour after dosing will be recorded for each dose.

3. LUM/IVA will be administered after all predose safety and PK assessments have been performed.
4. All LUM/IVA doses (morning and evening, as applicable) should be administered at approximately every 12 hours (± 1 hour) on each dosing occasion (e.g., if the morning dose is administered at 08:00 on Day 1, all subsequent morning doses should be administered between 07:00 and 09:00).
5. The granule formulation will be dispensed by opening the stick packs containing the granules and mixing the granules with the approved foods and liquids listed in the Study Reference Manual. Each dose will be composed of the approved food or liquids into which the granules from the stick packs are mixed. Details on preparing LUM/IVA will be provided in the Pharmacy Manual.
6. At the Day 1 Visit, all subjects will be observed for 4 hours after the morning LUM/IVA dose.
7. The morning dose on Day 15 will be the last LUM/IVA dose.

### 9.6.2 Part B

A review of safety, tolerability, and available PK data will be completed after Part A to confirm or adjust the dose(s) and/or weight bounds to be evaluated in Part B (Section 9.3.2). LUM/IVA will be administered orally as shown in Table 9-5.

**Table 9-5 Study Drug Administration: Planned Doses for Part B**

| Proposed Doses[a] | Time | LUM/IVA (Number of stick packs) |
|---|---|---|
| **Subject screening weight 7 to <10 kg[a,b]** | AM | 1 stick pack |
| LUM 75 mg/IVA 94 mg q12h | PM | 1 stick pack |
| **Subject screening weight 10 to <14 kg[a,b]** | AM | 1 stick pack |
| LUM 100 mg/IVA 125 mg q12h | PM | 1 stick pack |
| **Subject screening weight ≥14 kg[a,b]** | AM | 1 stick pack |
| LUM 150 mg/IVA 188 mg q12h | PM | 1 stick pack |

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

[a] The doses and weight bounds listed above are those planned for Part B. Depending on the results from Part A (e.g., Cohort 1 and Cohort 2), any changes to study drug dose(s) and/or weight bounds will be communicated to site personnel through a memorandum entitled "Justification for Dose Selection" to ensure clarity and consistency in study conduct.

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

LUM/IVA will be administered within 30 minutes from the start of consuming fat-containing food such as a standard "CF" high-fat, high-calorie meal or snack according to the following guidelines:

1. All doses of LUM/IVA (morning and evening, as applicable) should be administered at approximately every 12 hours (± 2 hours) on each dosing occasion (e.g., if the morning dose is administered at 08:00 on Day 1, all subsequent morning doses should be administered between 06:00 and 10:00).

2. The granule formulation will be dispensed by opening the stick packs containing the granules and mixing the granules with the approved foods and liquids listed in the Study Reference Manual. Each dose will be composed of the approved food or liquids into which the granules from the stick packs are mixed. Details on preparing LUM/IVA will be provided in the Pharmacy Manual.
3. On Day 1 Visit, all subjects will be observed for 4 hours after the LUM/IVA dose.
4. The date, dose quantity, time of drug administration, including whether food was taken with each dose, and occurrence and time of regurgitation within 1 hour after dosing, will be recorded for 1 day (i.e., 2 doses) before PK sample collection and on the days of PK sample collection.
5. On days of scheduled study visits (Day 1, Day 15, and during Weeks 4, 8, 12 and 16), with the exception of afternoon visits addressed below, the morning dose will be administered at the clinic after any predose assessments have been completed.
6. If the scheduled study visit occurs in the afternoon, the following guidelines must be used for administering either the morning or evening dose:
    - If the morning dose occurs within 6 hours of the study visit, the subject should withhold the dose at home, and administer the dose at the clinic.
    - If the morning dose occurs more than 6 hours before the study visit, the subject should take the morning dose at home, and the evening dose will be administered in the clinic. In this event, all assessments will be collected relative to the evening dose.
7. For visits after the Day 1 Visit, subjects will be instructed to bring all used and unused LUM/IVA materials to the site; LUM/IVA will be dispensed at each visit, as appropriate.
8. At the Week 24 Visit, the LUM/IVA dose will NOT be administered. The last LUM/IVA dose in Part B will be the previous dose administered before the Week 24 Visit.

## 9.7 Dose Modification for Toxicity

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

## 9.8 Removal of Subjects

Subjects may withdraw from the study at any time at the request of the parent or legal guardian. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. If a subject has been withdrawn from study drug treatment, the subject will continue to be followed as described in Section 9.1.6.1 (**Part A**) and Section 9.1.6.2 (**Part B**), provided that the subject's parent or legal guardian has not withdrawn consent.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject's parent or legal guardian. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject's parent or legal guardian return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit, if applicable (see Section 9.1.5), and follow up with the subject's parent or legal guardian regarding any unresolved AEs.

If the subject's parent or legal guardian withdraws consent for the study, no further evaluations should be performed, and no additional data should be collected. Vertex may retain and continue using the study data and samples after the study is over and may use the samples and information in the development of the study compound, and for other drugs and diagnostics, in publications and presentations, and for education purposes. If the subject's parent or legal guardian withdraws the subject from the study, the study data and samples collected will remain part of the study. A subject's parent or legal guardian will not be able to request the withdrawal of the subject's information from the study data. A subject's parent or legal guardian may request destruction of the samples collected from the subject during the study as long as those samples can be identified as the subject's samples.

### 9.9 Replacement of Subjects

#### 9.9.1 Part A

Subjects who withdraw or are withdrawn for nonsafety reasons during the study drug Treatment Period may be replaced at Vertex's discretion.

#### 9.9.2 Part B

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

## 10 STUDY DRUG INFORMATION AND MANAGEMENT

### 10.1 Preparation and Dispensing

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

### 10.2 Packaging and Labeling

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

### 10.3 Study Drug Supply, Storage, and Handling

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

**Table 10-1 Study Drug**

| Drug Name | Formulation/ Route | Packaging (Formulation Strength) | Storage Condition |
|---|---|---|---|
| LUM/IVA | Granules/ Oral | Supplied as 75-mg LUM/94-mg IVA granules in 1 stick pack | Store at ≤25°C (77°F) with excursions to 30°C (86°F) |
| LUM/IVA | Granules/ Oral | Supplied as 100-mg LUM/125-mg IVA granules in 1 stick pack | Store at ≤25°C (77°F) with excursions to 30°C (86°F) |
| LUM/IVA | Granules/ Oral | Supplied as and 150-mg LUM/188-mg IVA granules in 1 stick pack | Store at ≤25°C (77°F) with excursions to 30°C (86°F) |

IVA: ivacaftor; LUM: lumacaftor

## 10.4 Drug Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of (1) study drug received; (2) study drug dispensed to the subjects; and (3) study drug returned by the subject's parent or legal guardian. The subject's parent or legal guardian will be instructed to return all used and unused materials associated with the study drug to the site. These materials will be retained at the site according to instructions provided by Vertex or its designee. The study monitor will review study drug records and inventory throughout the study. If a site uses a site-specific Drug Accountability System and/or process, including processes associated with the destruction of returned materials, the process must be documented and approved by Vertex. The study monitor must review the drug accountability documentation on a regular basis. The study monitor will promptly communicate to Vertex any discrepancies he or she is unable to resolve with the site.

## 10.5 Disposal, Return, or Retention of Unused Drug

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

## 10.6 Compliance

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

If there is continued noncompliance of study drug dosing despite educational efforts, the investigator should contact the medical monitor to discuss discontinuation of the subject from the study treatment.

## 10.7 Blinding and Unblinding

This will be an open-label study. However, the site and the subject's parent or legal guardian should not be informed of a subject's study related sweat chloride (with the exception of results that are needed to establish eligibility when an historical sweat chloride measurement is not available), [redacted] results during the study even if the subject permanently discontinued treatment.

# 11 ASSESSMENTS

## 11.1 Timing of Assessments

The schedule of assessments is shown in Table 3-1, Table 3-2, and Table 3-3. In Part A, all assessments will be performed predose unless noted otherwise. In Part B, all assessments may be performed predose or postdose unless noted otherwise.

## 11.2 Subject and Disease Characteristics

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

Medical history will be elicited from each subject's parent or legal guardian during screening. Based on the medical history, the subject will be assessed for any disqualifying medical conditions as specified in the inclusion and exclusion criteria. The medical history should include a complete review of systems, past medical and surgical histories, and any known allergies. In addition, the subject's parent or legal guardian will be asked to provide the height of the subject's biological parents, if available.

See Section 11.4.2.1 for the sweat chloride assessment that will be performed during the Screening Visit in Part A (sweat chloride will be assessed during the Screening Visit, the Treatment Period, and the Safety Follow-up in Part B).

## 11.3 Pharmacokinetics

### 11.3.1 Blood Sampling

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

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

The actual times may change upon agreement of the clinical pharmacologist and investigator, but the number of samples will remain the same (**Part A only**). All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Samples collected outside of the acceptable windows will be considered protocol deviations. For each PK blood draw, a record of LUM/IVA administration will be collected as described in Section 9.6. The collection date and time that each PK blood sample is drawn will also be recorded.

If appropriate, these samples may also be used for the evaluation of metabolites that arise during treatment, for further evaluation of the bioanalytical method, and/or for analyses that provide

information on the metabolic pathways used by, or impacted by, LUM or IVA. These data will be used for exploratory purposes and may not be included in the clinical study report.

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

### 11.3.2 Processing and Handling of Pharmacokinetic Samples

Detailed procedures for the collection of blood samples and further procedures for processing and handling of samples for PK analysis will be provided in the Laboratory Manual.

### 11.3.3 Bioanalysis

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

## 11.4 Pharmacodynamics

### 11.4.1 Part A

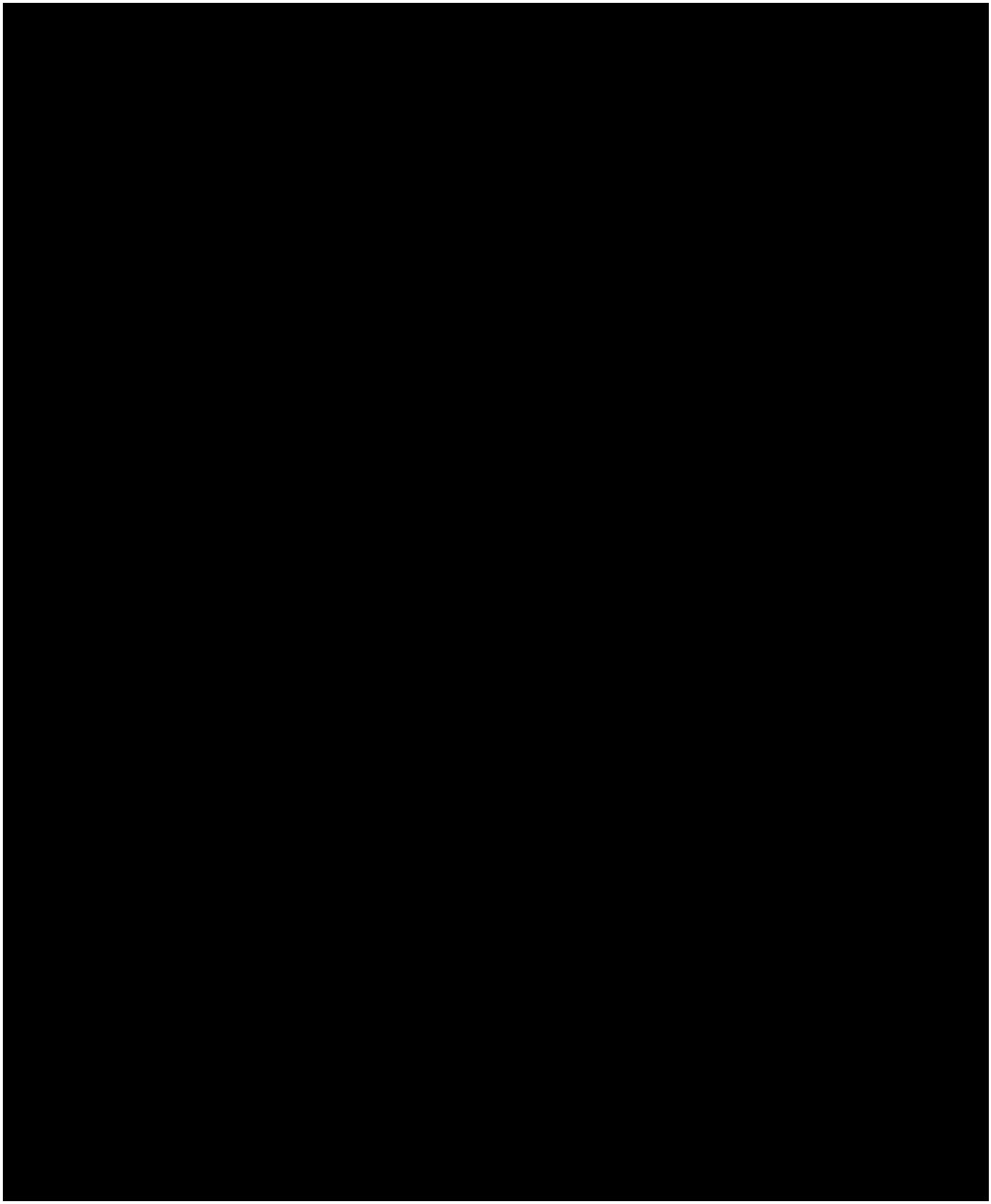
Not applicable

### 11.4.2 Part B

The assessments described in Section 11.4.2.1 through Section 11.4.2.8 will be performed in Part B.

#### 11.4.2.1 Sweat Chloride

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



## 11.5 Efficacy

### 11.5.1 Part A

Not applicable

### 11.5.2 Part B

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

## 11.6 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, pulse oximetry, ECGs, physical examinations (PEs), and ophthalmologic examinations (**Part B only**).

### 11.6.1 Adverse Events

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

### 11.6.2 Clinical Laboratory Assessments

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

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

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

**Table 11-1 Safety Laboratory Test Panels**

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

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

CF Genotype (Screening Period only): If a historic genotype result is not available at screening or if the historic genotype result is not approved by the Vertex medical monitor, CF genotyping will be performed on a subject to confirm the subject is homozygous for *F508del*.
Note: Newborn screening genotype results are not sufficient for eligibility.

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

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

### 11.6.3 Elevation of Liver Function Test Parameters

Mandatory Liver Function Testing

Liver function testing (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], alkaline phosphatase [ALP], and total bilirubin) must be performed while subjects are receiving LUM/IVA treatment (see Table 3-2, Table 3-3, and Section 11.6.2). These blood samples should be processed and shipped immediately as per the Laboratory Manual.

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

Study Drug Interruption

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

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

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

Resumption of Study Drug

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

Discontinuation of Study Drug

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

### 11.6.4 Physical Examinations and Vital Signs

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

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

An abbreviated PE will be performed at select study visits (see Table 3-2 and Table 3-3). The abbreviated PE will include an assessment of the following body systems: head/neck/thyroid, EENT, cardiovascular system, respiratory system, skin, and abdomen.

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

Weight and length will be assessed; BMI and weight-for-length will be derived. Length and weight must be measured with the subject in a dry diaper or dry underclothes only. Length should be measured while the subject is supine by measuring from the crown of the head to the bottom of the feet, with the hips and legs straightened. BMI will be calculated using the following equation: BMI ($kg/m^2$) = body weight (kg) ÷ length$^2$ ($m^2$).

### 11.6.5 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout. Additional standard 12-lead ECGs will be performed at any other time if clinically indicated. The performance of all ECGs will adhere to the following guidelines:

- The subject should rest for at least 5 minutes, if possible, before having an ECG performed.

- The ECG will be performed before any other procedures that may affect heart rate, such as blood draws.

The ECG traces will be manually read at the study site at the Screening Visit and Safety Follow-up Visit. A printout of the ECG traces will be made for safety review by the investigator and maintained with source documentation. All traces will be centrally evaluated by a qualified pediatric cardiologist. Clinically significant ECG abnormalities occurring during the study through the Safety Follow-up Visit will be recorded as AEs.

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

### 11.6.6 Ophthalmologic Examination

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

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

### 11.6.7 Contraception and Pregnancy

Not applicable

## 12 STATISTICAL AND ANALYTICAL PLANS

### 12.1 Sample Size and Power

**Part A**

Approximately 10 subjects are planned for enrollment. No formal sample size calculations have been performed. The number of subjects in Part A is common in early clinical pharmacology studies and is considered sufficient to achieve the PK objectives of Part A.

**Part B**

Approximately 30 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 27 subjects will complete Part B. No formal sample size calculations have been performed. The number of subjects in Part B is deemed adequate to meet the primary safety objective.

Table 12-1 displays estimates of the probability for observing AEs in at least 1 subject for the given incidence (θ) and sample size. With a total sample size of 27 subjects (completers), there is a 75.0% chance of observing AEs in at least 1 subject if the true incidence rate is 5%, and a 94.2% chance of observing AEs in at least 1 subject if the true incidence rate is 10%.

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

| Sample Size | θ = 5% | θ = 10% |
|---|---|---|
| 27[a] | 75.0% | 94.2% |

[a] 27 reflects the sample size of the completers.

## 12.2 Analysis Sets

**Part A**

**All Subjects Set** is defined as all subjects who have signed informed consent and enrolled or dosed in Part A.

**Safety Set** will include all subjects who received at least 1 dose of study drug in Part A. The safety analyses will be based on the Safety Set overall, unless otherwise specified. In addition, the summary by the initial dosing groups (LUM 75 mg/IVA 94 mg q12h, LUM 100 mg/IVA 125 mg q12h, and LUM 150 mg/IVA 188 mg q12h) at enrollment determined by weight at the Screening Visit will be provided as supplementary information.

**Part B**

**All Subjects Set** is defined as all subjects who have signed informed consent and enrolled or dosed in Part B.

**Safety Set** will include all subjects who received at least 1 dose of study drug in Part B. The safety analyses will be based on the Safety Set overall, unless otherwise specified. If the 3 weight-based doses are used in Part B, the summary by the initial dosing groups (LUM 75 mg/IVA 94 mg q12h, LUM 100 mg/IVA 125 mg q12h, and LUM 150 mg/IVA 188 mg q12h) at enrollment determined by weight at the Screening Visit will be provided as supplementary information.

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

[redacted]

**Part A and Part B**

Subject data listings will be referenced using the All Subjects Set in the corresponding part, unless otherwise specified.

## 12.3 Statistical Analysis

This section presents a summary of the planned statistical analyses of safety for Part A and the planned statistical analysis of safety and PD for Part B. The Vertex Biometrics Department, or designee, will analyze the data derived from this study.

Statistical analysis and presentation details will be provided in the statistical analysis plans (SAPs) for the corresponding parts. [redacted] The SAPs will be finalized before the data cut/lock for each part.

### 12.3.1 General Considerations

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

Part A data will be summarized overall and by cohort. The Part A primary safety conclusion will be based upon the overall group. Part B will be summarized overall.

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

**Categorical variables** will be summarized using counts and percentages.

**Baseline value**, unless specified otherwise, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug.

For Part B only:

- For sweat chloride, the values at each visit will be based on the averaged measurements from left and right arms as specified in Section 12.3.3.2.1. The baseline will be defined as the average of the values at screening and the pretreatment measurement on Day 1. If only 1 pre-first dose measurement of sweat chloride is available, that measurement will be considered the baseline.

**Change (absolute change) from baseline** will be calculated as Postbaseline value − Baseline value.

**Relative change from baseline** will be calculated and expressed in percentage as 100% × (Postbaseline value − Baseline value)/Baseline value.

The **Treatment-emergent (TE) Period** will include the time from the initial dose in Treatment Period in each part to the Safety Follow-up Visit or 14 days after the last dose of the study drug in the corresponding part, whichever occurs first.

### 12.3.2 Background Characteristics

Unless otherwise specified, this section applies to both Part A and Part B. All summaries will be based on the Safety Set of the corresponding part overall. No statistical hypothesis testing will be performed.

#### 12.3.2.1 Subject Disposition

The number of subjects in the following categories will be summarized:

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

The number and percentage (based on Safety Set) of subjects in each of the following disposition categories will be summarized:

- Completed treatment
- Prematurely discontinued the treatment and the reason for discontinuation
- Completed study (i.e., completed Safety Follow-up Visit)

- Prematurely discontinued the study and the reason for discontinuation
- Enrolled in a rollover extension study

[redacted]

A listing will be provided for subjects who discontinued treatment or who discontinued study with reasons for discontinuation. A listing of subjects enrolled in each part will be provided.

#### 12.3.2.2 Demographics and Baseline Characteristics

Demographics, medical history, and baseline characteristics will be summarized. For Part A, sweat chloride at screening will be listed. Important protocol deviations will be provided as a subject data listing only. The rules used to define the important protocol deviations will be provided in the SAPs.

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

[redacted]

#### 12.3.2.3 Prior and Concomitant Medications

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

**Prior medication:** any medication that started before the first dose date of study drug in each study part, regardless of when the medication ended.

**Concomitant medication:** medication continued or newly received on or after the first dose date of study drug of a study part through the end of the TE Period of the corresponding study part.

**Post-treatment medication:** medication continued or newly received after 14 days after the last dose of study drug in each study part.

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

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

#### 12.3.2.4 Study Drug Exposure

Duration of study drug exposure (in days) will be calculated as follows: last dose date – first dose date + 1 day, regardless of any study drug interruption. If the last dose date of study drug is missing, the subject's last exposure date will be used for analysis purposes.

**Part A**

Study drug exposure duration will be summarized overall based on the Part A Safety Set.

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

**Part B**

Study drug exposure duration will be summarized overall based on the Part B Safety Set and descriptively as a quantitative variable (number, mean, SD, SE, median, minimum, and maximum).

Additionally, the cumulative duration of treatment exposure, defined as the sum of the subject's duration of treatment exposure and expressed in subject-years, will be provided. Duration of exposure will also be summarized as a categorical variable.

#### 12.3.2.5 Study Drug Compliance

**Part A**

Compliance will be presented in an individual subject data listing.

**Part B**

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

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

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

Study drug compliance will be based on Part B Safety Set overall.

### 12.3.3 Pharmacodynamics Analysis (Part B Only)

#### 12.3.3.1 Analysis of Primary Endpoints

Not applicable.

#### 12.3.3.2 Analysis of Secondary Pharmacodynamic Endpoint

Analyses for the secondary PD endpoint are described in Section 12.3.3.2.1. [redacted]

#### 12.3.3.2.1 Absolute Change From Baseline in Sweat Chloride at Week 24

For each subject and at each time point, 2 sweat chloride measurements will be collected: 1 from the right arm and 1 from the left arm. Of the 2 measurements, only the sweat chloride value obtained from a sample volume ≥15 µL will be included in any analysis (i.e., for samples with

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

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

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

[redacted]

[redacted]

### 12.3.4 Safety Analysis

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

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

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (serum chemistry and hematology)
- ECGs (standard 12-lead)
- Vital signs
- Pulse oximetry
- Ophthalmologic examinations (Part B only)

For Part A and Part B, safety endpoints will be analyzed based on the Safety Set for the corresponding part.

Subgroup analysis or any additional analysis will be described in the SAP.

#### 12.3.4.1 Adverse Events

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

- **Pretreatment AE:** any AE that started before the first dose date of study drug in a study part.
- **TEAE**: any AE that increased in severity or that was newly developed at or after the first dose of study drug through the end of the TE Period of each corresponding study part.
- **Post-treatment AE**: any AE that increased in severity or that newly developed after the TE Period of each corresponding study part.

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

Details for imputing missing or partial start dates of adverse events are described in the SAP.

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

An overview of the TEAE profile will be provided, including total number of TEAEs, with number and percentage of subjects for the following categories: (1) All TEAEs, (2) Grades 3/4 TEAEs, (3) TEAEs by relationship to study drug, (4) TEAEs by maximum severity, (5) TEAEs

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

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

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

Summaries will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT) using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries.

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

#### 12.3.4.2 Clinical Laboratory Assessments

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

The number and percentage of subjects meeting a threshold analysis criterion during the TE Period will be summarized for each part. The threshold analysis criteria and the parameter selection criteria will be provided in the SAP.

For hematology and chemistry, the number and percentage of subjects with abnormal low (<lower limit of normal [LLN]) value and with abnormal high (>ULN) value at each scheduled time point will be summarized.

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

#### 12.3.4.3 Electrocardiogram

For treatment-emergent ECG measurements, a summary of raw values and change from baseline values will be provided at each scheduled time point for the following standard 12-lead ECG measurements: RR (msec), HR (beats per minute), PR (msec), QRS duration (msec), QRS axis (degrees), QT (msec), and QT corrected for HR intervals. In addition, the mean value (95% CI) at each time point will be plotted for QTc.

The number and percentage of subjects meeting a threshold analysis criterion during the TE Period will be summarized. The threshold value criteria will be provided in the SAP.

#### 12.3.4.4 Vital Signs

For treatment-emergent vital signs measurements, the raw values and change from baseline values will be summarized at each visit: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), respiratory rate (breaths per minute), weight, length, and BMI.

The number and percentage of subjects meeting a threshold analysis criterion during the TE Period will be summarized. The threshold value criteria will be provided in the SAP.

#### 12.3.4.5 Pulse Oximetry

For treatment-emergent pulse oximetry measurements, a summary of raw values and change from baseline values will be provided at each scheduled time point for the percent of oxygen saturation by pulse oximetry.

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

#### 12.3.4.6 Ophthalmologic Examinations

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

#### 12.3.4.7 Physical Examination

PE findings will be presented as an individual subject data listing only.

### 12.3.5 Interim and IDMC Analyses

#### 12.3.5.1 Interim Analysis

Interim analyses may take place at any time during the study if deemed necessary by the Vertex team.

#### 12.3.5.2 IDMC Analysis

Details of the IDMC (Section 9.1.7) analysis will be provided in the IDMC Analysis Plan.

## 12.4 Clinical Pharmacology Analysis

### 12.4.1 Pharmacokinetic Analysis

Nonlinear mixed effects modeling will be applied for the PK analysis of LUM and IVA. Covariates (e.g., body weight) will be evaluated and included in the final population PK model if

including them significantly improves the overall model fit and the accuracy and precision of population estimates of PK parameters.

Preliminary analysis will be performed on the PK data obtained from Part A of the current study. The PK analysis, along with safety and tolerability data from Part A (e.g., after Cohort 1 and after Cohort 2), will be used to appropriately confirm the dose selection for Part B of the study (or adjust the doses if necessary before the start of Part B) based on PK parameters relative to historical results in the clinical development program. An interim PK analysis of data collected in Part A and Part B may be performed to inform future development of LUM and IVA. This interim analysis, if performed, will not affect the conduct of the present study. Plasma concentrations for LUM, IVA, and their metabolites will be summarized using descriptive statistics by visits and time points.

Details of the analyses will be provided in the clinical pharmacology analysis plan (CPAP).

### 12.4.2 Pharmacokinetic/Pharmacodynamic Analyses

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

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

Details of methods used will be provided in the CPAP.

## 13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

### 13.1.1 Adverse Events

#### 13.1.1.1 Definition of an Adverse Event

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

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

#### 13.1.1.2 Clinically Significant Assessments

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

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

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

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

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

#### 13.1.1.3 Documentation of Adverse Events

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

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit in Part A, 13 days after the last dose of study drug.
- For enrolled subjects who do not have a Safety Follow-up Visit in Part B, the earliest of
    - 18 days after the last dose of study drug, or
    - the ETT Visit, if that visit is 10 days or later following the last dose of study drug (see Section 9.1.6)

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

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

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

#### 13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007, Center for Biologics Evaluation and Research, http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm (Accessed August 2015). In considering the severity of an AE in a pediatric subject, the investigator will consider that reference ranges for pediatric clinical laboratory parameters may differ from those given in the vaccine scale. The severity of an AE that does not appear in this scale will be determined according to the definitions in Table 13-1.

**Table 13-1 Grading of AE Severity**

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

#### 13.1.1.5 Adverse Event Causality

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

**Table 13-2 Classifications for AE Causality**

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

#### 13.1.1.6 Study Drug Action Taken

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

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

| Classification | Definition |
|---|---|
| **Dose not changed** | Study drug dose not changed in response to an AE |
| **Dose reduced**[a] | Study drug dose reduced in response to an AE |
| **Drug interrupted** | Study drug administration interrupted in response to an AE |
| **Drug withdrawn** | Study drug administration permanently discontinued in response to an AE |
| **Not applicable** | Action taken regarding study drug administration does not apply.<br>"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. |

[a] Study drug dose cannot be reduced in this study (Section 9.7).

#### 13.1.1.7 Adverse Event Outcome

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

**Table 13-4 Classifications for Outcome of an AE**

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

#### 13.1.1.8 Treatment Given

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

### 13.1.2 Serious Adverse Events

#### 13.1.2.1 Definition of a Serious Adverse Event

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

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation in the study and is suspected of being a delayed toxicity due to administration of the study drug)

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

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the subject's parent or legal guardian signed the ICF, and the hospitalization or procedure was planned before the subject's parent or legal guardian 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 through the Safety Follow-up Visit, regardless of causality, will be reported by the investigator to Vertex Global Patient Safety (GPS). In addition, all SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours**.

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

#### 13.1.2.3 Reporting Serious Adverse Events

The investigator is responsible for notifying the sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. The SAE Form will be

completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

For questions, contact telephone: [redacted]

#### 13.1.2.4 Expedited Reporting and Investigator Safety Letters

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

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

### 13.2 Administrative Requirements

#### 13.2.1 Ethical Considerations

The study will be conducted in accordance with the current ICH GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, 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 subject's parents or legal guardians (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 legal representative or guardian before study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

#### 13.2.3 Investigator Compliance

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

When circumstances require an immediate departure from procedures set forth in the protocol, the investigator will contact Vertex to discuss the planned course of action. If possible, contact

will be made before the implementation of any changes. Any departures from the protocol will be fully documented in the source documentation and in a protocol deviation log.

### 13.2.4 Access to Records

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

### 13.2.5 Subject Privacy

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

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

### 13.2.6 Record Retention

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

### 13.2.7 Study Termination

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

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

- Subject or investigator noncompliance

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

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

### 13.2.8 End of Study

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

## 13.3 Data Quality Assurance

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

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

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

## 13.4 Monitoring

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

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

## 13.5 Electronic Data Capture

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

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

the study and will document the dates and details of study procedures, AEs, other observations, and subject status.

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

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

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

## 13.6 Publications and Clinical Study Report

### 13.6.2 Clinical Study Report

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

## 14 REFERENCE


1 Cystic Fibrosis Foundation. What is cystic fibrosis? Available at: https://www.cff.org/What-is-CF/About-Cystic-Fibrosis/. Accessed 07 February 2018.

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5 Kreindler JL. Cystic fibrosis: Exploiting its genetic basis in the hunt for new therapies. Pharmacol Ther. 2010;125(2):219-29.

6 Cystic Fibrosis Australia. Cystic Fibrosis in Australia 2014: 17th Annual Report From the Australian Cystic Fibrosis Data Registry. North Ryde, NSW, Australia: Cystic Fibrosis Australia; 2016.

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8 European Cystic Fibrosis Society. 2015 ECFS Patient Registry Annual Data Report. Karup, Denmark: European Cystic Fibrosis Society; 2017.

9 O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet. 2009;373(9678):1891-904.

10 Stick SM, Brennan S, Murray C, Douglas T, von Ungern-Sternberg BS, Garratt LW, et al. Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening. J Pediatr. 2009;155(5):623-28.

11 Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: A consensus statement. J Pediatr. 1998;132(4):589-95.

12 Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009;20(3):629-37.

13 ICH E11. Clinical Investigation of Medicinal Products in the Pediatric Population. 20 July 2000.

14 Vertex Pharmaceuticals Incorporated. Report N329. Population Pharmacokinetics of Lumacaftor and Ivacaftor in Subjects 2 Through 5 Years of Age with Cystic Fibrosis, Homozygous for *F508del*. Report date: 10 January 2018.

15 Vertex Pharmaceuticals Incorporated. Lumacaftor/Ivacaftor Investigator's Brochure, Version 3.0. Report date: 12 May 2017.


[redacted]

# 15 PROTOCOL SIGNATURE PAGES

## 15.1 Sponsor Signature Page

| Protocol #: VX16-809-122 | Version #: 2.0 | Version Date: 04 December 2019 |
|---|---|---|
| Study Title: A Phase 3, 2-part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for *F508del* | | |

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

[redacted]

## 15.2 Investigator Signature Page

| Protocol #: VX16-809-122 | Version #: 2.0 | Version Date: 04 December 2019 |
|---|---|---|
| Study Title: A Phase 3, 2-part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for *F508del* | | |

I have read Protocol VX16-809-122, Version 2.0, and agree to conduct the study according to its terms. I understand that all information concerning LUM/IVA and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date

## 1 TITLE PAGE

*VERTEX PHARMACEUTICALS INCORPORATED*

# Clinical Study Protocol Addendum for Cystic Fibrosis

## Cystic Fibrosis Studies for the Following Programs

[redacted]

**Lumacaftor/Ivacaftor (VX-809/VX-770)**

[redacted]

**Version and Date of Protocol Addendum:** Version 3.0, 29 July 2020
Replaces Version 2.0, dated 15 May 2020

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

## Summary of Changes to Cystic Fibrosis Clinical Study Protocols

Vertex is currently evaluating several CFTR modulators in clinical studies for the treatment of cystic fibrosis (CF), a serious and life-threatening disease. In completed studies, treatment with these CFTR modulators has generally resulted in rapid, robust, clinically meaningful, and statistically significant improvements in clinical measures, and are generally safe and well tolerated. Adverse events (AEs) seen with these treatments are mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects.

During this COVID-19 pandemic, the safety of the subjects, investigators, and site personnel participating in these clinical studies is Vertex's first priority, thus it is important to minimize any unnecessary risk to COVID-19 exposure through travel to study sites. This addendum summarizes the measures taken for ongoing CF clinical studies. These operational adjustments were implemented to align with Health Authority guidance ensuring the protection of subjects, investigators, and site personnel while maintaining compliance with GCP and minimizing impact to the integrity of the studies. Overall, the benefit-risk of these studies remains favorable.

Vertex recommends that subjects and sites refer to local guidance regarding travel restrictions. There are no operational changes to the study protocols for subjects who can travel to the study sites for their visits. However, to ensure continued safety of subjects who *cannot* travel to the study sites for their visits (for any reason due to COVID-19), specific alternative measures are being implemented to minimize the risk of exposure to COVID-19 (see table below). As the COVID-19 pandemic evolves, Vertex will continue to assess the need for additional actions to ensure the safety of all involved in these clinical studies.

Addendum Version 3.0 summarizes additional measures taken for these ongoing CF clinical studies (see table below) to ensure continued safety.

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Rationale for Change | Study Number |
|---|---|---|
| **Addendum Version 3.0, dated 29 July 2020** | | |
| **Assessments**<br><br>Unscheduled visit(s) will be permissible at the discretion of the investigator(s) or Vertex. The unscheduled visit(s) may be conducted at any time during the study (including after the protocol defined last study visit) in the event assessments specified to be collected at a scheduled visit were not collected due to COVID-19. | To ensure subject safety and/or to facilitate evaluation of safety and/or efficacy if assessments are not performed per the schedule in the protocol due to COVID-19. | [redacted]<br>[redacted]<br>VX16-809-122<br>[redacted]<br>[redacted]<br>[redacted]<br>[redacted] |
| Implementaion of measures described in addenda versions 1.0 and 2.0, as applicable. | To ensure subject safety and/or to facilitate evaluation of safety and/or efficacy while maintaining study integrity and the safety of subjects and site personnel. | [redacted] |

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Rationale for Change | Study Number |
|---|---|---|
| **Addendum Version 2.0, dated 15 May 2020** | | |
| **Assessments**<br><br>Weight and height/length/stature may be assessed by subjects or their caregivers using medical grade scales and stadiometers, as indicated per protocol and per local regulation. Sites and subjects will receive training and guidance as needed on these devices.<br><br>Subjects or caregivers will provide these measurements to site personnel by telephone or video call. Investigators will review results and contact subjects for follow-up as needed. All data will continue to be retained in the subject's source files. | To allow for collection of key data to assess safety and/or efficacy while maintaining study integrity and the safety of subjects and site personnel.<br><br>*Addendum 1 allowed for these assessments to be performed by qualified personnel conducting the in-home visits. Addendum 2 allows for these assessments to be performed by subjects or caregivers.* | [redacted]<br><br>[redacted]<br><br>VX16-809-122<br>[redacted]<br><br>[redacted]<br><br>[redacted]<br><br>[redacted]<br><br>[redacted] |

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Protocol Change | Protocol Change |
|---|---|---|
| **Addendum Version 1.0, dated 24 April 2020** | | |
| **Consenting of Subjects**<br>ICFs may be provided electronically or by post mail to subjects (and/or caregivers, as indicated per protocol). The subjects and/or caregivers will review the ICF with an appropriately qualified member of the investigator's team via telephone contact or video call. After this review, subjects and/or caregivers will consent (or assent, if applicable), and/or reconsent verbally and by signing and dating the ICF and returning it to the site via post mail. The signed and dated ICF will then be signed and dated by the investigator.<br><br>Subjects participating in select studies may have the opportunity to enroll in longterm extension studies. Informed consent (or assent, if applicable), and/or reconsent for subjects (and/or caregivers, as indicated per protocol) may be obtained per the same process described above, as applicable. | To provide alternative methods of obtaining reconsent or consent, as applicable, while ensuring subject safety. | [redacted]<br>[redacted]<br>VX16-809-122<br>[redacted]<br>[redacted] |
| **Study Drug Shipping**<br>Study drug may be shipped directly from the site to the subject, as applicable, and if permitted by local regulations; subject protected health information will not be released to Vertex.<br><br>Reconciliation, return, and destruction of study drug will continue to occur at the clinical site as indicated per protocol and in adherence to local regulations. | To ensure subjects can continue treatment with study drug without interruption while ensuring their safety.<br><br>To clarify that despite these alternative measures, reconciliation, return, and destruction of study drug will remain as indicated per protocol. | [redacted] |
| **In-home Visits and/or Telephone Contact**<br>Study visits may be conducted as in-home visits by qualified personnel as requested by participating sites on a per-subject basis. In addition, all subjects may be contacted by site personnel by telephone or video call, irrespective of in-home visits. | To provide subjects the opportunity to continue participation in the clinical studies while ensuring their safety by minimizing the risk to COVID-19 exposure through travel. | [redacted]<br>[redacted]<br>[redacted]<br>for telephone contact only |

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Protocol Change | Protocol Change |
|---|---|---|
| **Addendum Version 1.0, dated 24 April 2020** | | |
| **Safety Assessments and Reporting**<br>Safety assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits (e.g., personnel from site or qualified health care agency). These assessments may include the following, as indicated per protocol, and per local regulation:<br>• vital signs<br>• pulse oximetry<br>• height/length/stature<br>• weight<br>• physical examination (complete or abbreviated)<br>• pregnancy test (serum or urine)<br>• urinalysis<br>• blood draws for safety test panels (chemistry, LFT panel, lipid panel, hematology, coagulation).<br>Blood and/or urine samples for safety assessments are analyzed as indicated per protocol for subjects who have in-home visits.<br>Blood and/or urine samples for safety assessments may be collected and analyzed at local laboratories for subjects who do not have in-home visits, but do not complete the assessment at the site.<br>In addition, safety assessents will be evaluated by telephone. These assessments may include the review of the following:<br>• AEs<br>• signs and symptoms/systems for CF<br>• medications<br>• planned or unplanned hospitalizations for CF<br>• study drug administration<br>• outcomes related to PEx<br>• outcomes related to antibiotic treatment<br>Investigators will review results (in-home and telephone) and contact subjects for follow-up as needed.<br>All data will continue to be retained in the subject's source files.<br>Any clinically significant finding (e.g., AE, SAE, laboratory abnormalities) will continue to be reported as indicated per protocol. | To assess the safety and tolerability of the CFTR modulator evaluated in the specific clinical study while ensuring subject safety. These safety assessments will continue to provide safety data while minimizing burden to subjects and site personnel.<br><br>To clarify that despite these alternative measures, all adverse events and serious adverse events should be reported as indicated per protocol. | [redacted]<br>[redacted]<br>VX16-809-122<br>[redacted]<br>[redacted]<br>[redacted]<br>[redacted]<br>[redacted]<br>[redacted]<br>for telephone contact and blood samples collected and analyzed at local laboratories |

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Protocol Change | Protocol Change |
|---|---|---|
| **Addendum Version 1.0, dated 24 April 2020** | | |
| **Efficacy and Other Assessments**<br>Efficacy and other assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits. These assessments may include the following, as indicated per protocol, and per local regulation.<br><br>In-home Spirometry Assessment<br>A spirometry device may be provided to subjects for in-home assessments of lung function as indicated per protocol. Sites and subjects will receive training and guidance as needed.<br><br>[redacted]<br><br>Other Assessments<br>• ECGs<br>• sweat chloride<br>• blood samples for *CFTR* genotype testing, [redacted] PK, FSH, [redacted] biomarkers, and vitamin levels<br>[redacted] | To be able to assess safety, treatment effectiveness, and quality of life measures of the CFTR modulator evaluated in the specific clinical study while ensuring subject safety. | All Efficacy and Other Assessments<br>[redacted]<br><br>VX16-809-122<br>[redacted] |

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Protocol Change | Protocol Change |
|---|---|---|
| **Addendum Version 1.0, dated 24 April 2020** | | |
| **Remote Monitoring**<br>Vertex has implemented remote monitoring visits where applicable, including remote source data verification, as allowed per local regulations. Remote monitoring will focus on collection of safety data, and data supporting primary and key secondary endpoints. | To allow for review of key data to inform on the safety of subjects receiving treatment.<br><br>To allow for review of other key data to inform on the objectives of the study while maintaining study integrity and the safety of subjects and site personnel. | [redacted]<br><br>[redacted]<br>VX16-809-122<br>[redacted]<br><br>[redacted]<br><br>[redacted]<br><br>[redacted]<br><br>[redacted] |

AE: adverse event; CF: cystic fibrosis; [redacted] ECG: electrocardiogram; [redacted] FSH: follicle-stimulating hormone; GCP: Good Clinical Practice; ICF: informed consent form; [redacted] LFT: liver function test; PEx: pulmonary exacerbation; PK: pharmacokinetic; SAE: serious adverse event; [redacted]