1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number: VX15-809-115 (Final Analysis - Part A)

A Phase 3, 2-Part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation.

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2 TABLE OF CONTENTS

4 INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis of study VX15-809-115 Part A only and is based on the

- approved clinical study protocol, dated 01 August 2016, Version 2.0,
- approved eCRF, dated 08 June 2016, Version 2.0.

Study VX15-809-115 is a phase 3, 2-part, open-label study to evaluate the safety and pharmacokinetics of lumacaftor/ivacaftor combination therapy in subjects aged 2 through 5 years with cystic fibrosis, homozygous for the *F508del-CFTR* mutation.

This SAP (Methods) documents the planned final safety analysis and data presentation for Part A of VX15-809-115.

SAS® Version 9.2 Software (SAS Institute, Cary, North Carolina, USA) or higher will be used to generate all statistical outputs (tables, figures, listings and datasets).

The SAP will be finalized and approved before the end of Part A with CRFs locked on individual subject basis for the final analysis of Part A. Any changes made to the SAP Methods after the above end of Part A activity has occurred will be documented in the clinical study report for this study.
The analysis addressing the pharmacokinetic (PK) objective of the study will be described in the Clinical Pharmacology Analysis Plan (CPAP) which will be developed separately by the Clinical Pharmacology department at Vertex Pharmaceuticals Incorporated (Vertex).

5 STUDY OBJECTIVES

5.1 Primary Objective

Part A

To evaluate the PK of lumacaftor (LUM) and ivacaftor (IVA) and their respective metabolites in subjects aged 2 through 5 years with cystic fibrosis (CF), homozygous for *F508del*

Part B

To evaluate the safety of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for *F508del*

5.2 Secondary Objectives

Part A

To evaluate the safety of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for *F508del*

Part B

- To evaluate the pharmacodynamics (PD) of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for *F508del*
- To evaluate the off-drug PD response after the Washout Period
- To evaluate the PK of LUM and IVA and their respective metabolites in subjects aged 2 through 5 years with CF, homozygous for *F508del*

5.3 Other Objectives

Not Applicable

6 STUDY ENDPOINTS

6.1 Primary Endpoint

Part A

PK parameters of LUM and IVA

Part B

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

6.2 Secondary Endpoints

Part A

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

Part B

- Absolute change from baseline in sweat chloride at Week 24
- Absolute change from baseline in body mass index (BMI) and BMI-for-age z-score at Week 24
- Absolute change from baseline in weight and weight-for-age z-score at Week 24
- Absolute change from baseline in stature and stature-for-age z-score at Week 24
- Time-to-first pulmonary exacerbation through Week 24
- Number of pulmonary exacerbations through Week 24
- Number of CF-related hospitalizations through Week 24

- Absolute change in fecal elastase-1 (FE-1) levels from baseline at Week 24
- Absolute change in serum levels of immunoreactive trypsinogen (IRT) from baseline through Week 24
- Change in microbiology cultures from baseline at Week 24
- Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at Week 24
- Absolute change in sweat chloride from Week 24 at Week 26
- Acceptability/palatability of LUM/IVA granules at Day 1
- Absolute change from baseline in lung clearance index $(LCI)_{2.5}$ at Week 24
- Absolute change from baseline in $LCI_{5.0}$ at Week 24
- PK parameters of LUM, IVA, and their respective metabolite

7 STUDY DESIGN

7.1 Overall Design

This is a Phase 3, 2-part, open-label, multicenter study evaluating the PK, safety, tolerability, and PD of multiple doses of LUM/IVA in subjects 2 through 5 years of age (inclusive) with CF, homozygous for *F508del*. Part A is designed to evaluate the PK of LUM and IVA and their respective metabolites and the safety of LUM/IVA combination therapy. Part B is designed to evaluate the safety and PD of LUM/IVA combination therapy and also to evaluate the PK of LUM and IVA and their respective metabolites.

Subjects who participate in Part A may participate in Part B, if they meet the eligibility criteria.

Part A

Approximately 12 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 10 subjects should complete Part A. Approximately half of the subjects should complete the study in each of the following weight groups: <14 kg and ≥14 kg at screening.

Part A includes the following:

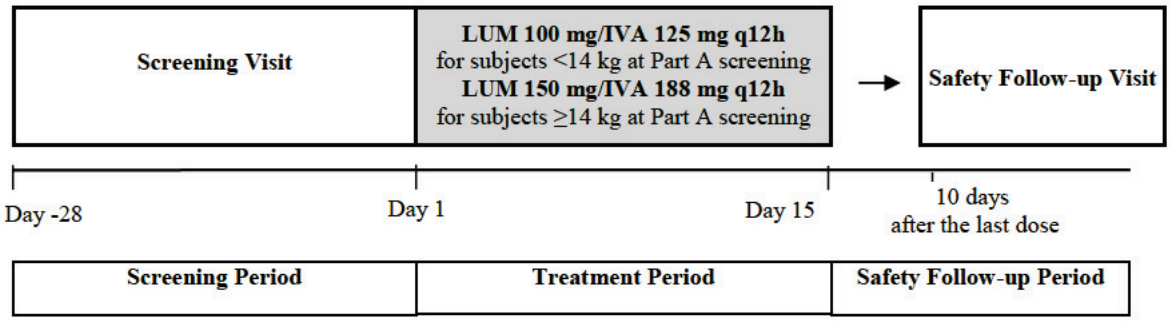
- Screening Period (Day -28 through Day -1)
- Treatment Period (Day 1 through Day 15 ± 2 days)
- Safety Follow-up Visit (10 ± 3 days after the last dose of LUM/IVA)

Figure 7-1 depicts the schematic for the Part A study design.

A review of safety, tolerability, and available PK data will be completed by an internal Vertex team after Part A to determine the dose(s) to be evaluated in Part B. Additional subjects or treatment cohorts may be enrolled, if data from the initial, planned, 12 subjects are inadequate to make a determination of the dose(s) to be evaluated in Part B.

In the later sections, all discussions and analyses plans will be limited to Part A only.

Figure 7-1 Schematic of Study Design for Part A



IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours
Notes: Approximately half of the subjects should complete the study in each of the following weight groups: <14 kg and ≥14 kg at screening. No dose adjustments will be made across the duration of study treatment. On Day 15, only the morning dose of LUM/IVA will be administered.

Part B

Approximately 56 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 50 subjects should complete Part B; at least 10 subjects must be <3 years of age at screening. Subjects should be ≥3 years of age at screening for enrollment in the optional LCI Substudy at a subset of sites. Additional subjects may be enrolled at the sponsor's discretion to achieve up to 30 subjects in the LCI Substudy.

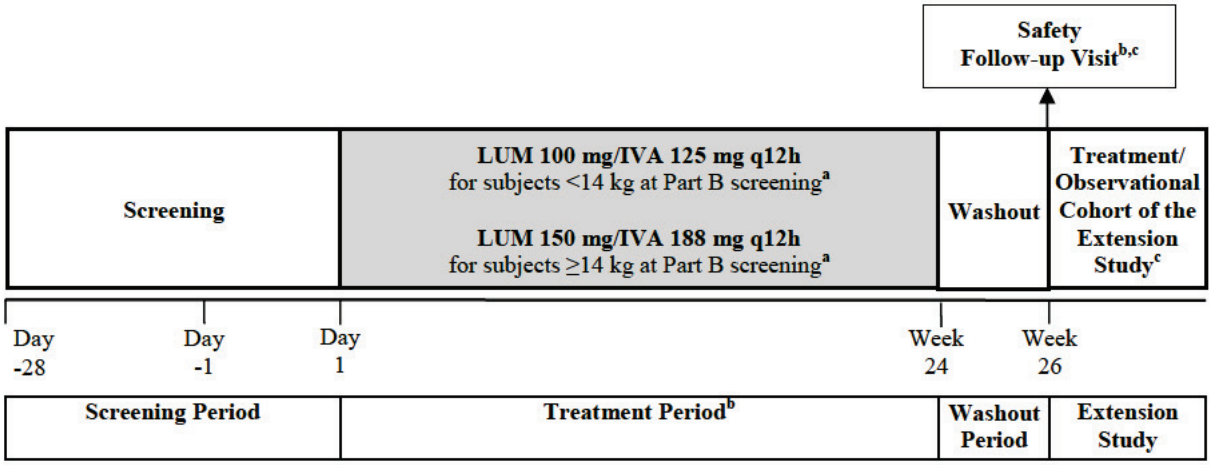
Part B includes the following:

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

Figure 7-2 depicts the schematic for the Part B study design.

Subjects who have completed the required visits in Part B may be eligible to enroll in the Treatment Cohort or Observational Cohort of an Extension Study to evaluate long-term treatment with LUM/IVA; enrollment will be based on the eligibility criteria. The Treatment Cohort will enroll subjects who completed LUM/IVA treatment and the Safety Follow-up Visit in Part B. The Observational Cohort will enroll subjects who received at least 4 weeks of LUM/IVA treatment in Part B and completed visits up to the Safety Follow-up Visit, if applicable, in Part B, but do not meet eligibility criteria for enrollment into the Treatment Cohort. 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.

Figure 7-2 Schematic of Study Design for Part B



ETT: Early Termination of Treatment; IVA: ivacaftor; LCI: lung clearance index; LUM: lumacaftor; q12h: every 12 hours
Notes: Approximately 56 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 50 subjects should complete Part B; at least 10 subjects must be <3 years of age. Subjects should be ≥3 years of age for enrollment in the optional LCI Substudy at a subset of sites. Additional subjects may be enrolled at the sponsor's discretion to achieve up to 30 subjects in the LCI Substudy.

[a] The doses listed above are the planned doses for Part B. Depending on the results from Part A, a single dose from Part A may be selected for all subjects in Part B or a previously unspecified dose or doses may be selected for Part B. No dose adjustments across the duration of treatment will be made. The last dose of LUM/IVA in Part B will be the evening dose before the Week 24 Visit.

[b] Subjects who prematurely discontinue LUM/IVA treatment will be asked to complete the ETT Visit, to remain on study, and to complete the study assessments from the time of LUM/IVA discontinuation through the Week 24 Visit and the Safety Follow-up Visit, if applicable. The Safety Follow-up Visit is not required for subjects who permanently discontinue LUM/IVA treatment before or at the Week 16 Visit if they return for the Week 24 Visit or for 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 ETT Visit.

[c] Subjects who have completed the required visits in Part B may be eligible to enroll in the Treatment Cohort or Observational Cohort of an Extension Study to evaluate long-term treatment with LUM/IVA; enrollment will be based on the eligibility criteria.

7.2 Sample Size and Power

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

7.3 Randomization

Part A is an open-label study with weight-based treatment group assignment. Randomization is not required in this Part.

7.4 Blinding and Unblinding

This is an open-label study. However for Part A, subjects and their legally appointed and authorized representative (e.g., parent or legal guardian) should not be informed of their study-related spirometry (subjects ≥3 years of age at corresponding part's screening) during the study, regardless if the subject permanently discontinues treatment.

8 ANALYSIS SETS

8.1 All Subjects Set

All Subjects Set is defined as all subjects who have signed informed consent (and assent, if applicable) and enrolled or dosed in Part A. This analysis set will be used for all individual subject data listings and the disposition summary table, unless specified otherwise.

8.2 Safety Set

Safety Set will include all subjects who received at least 1 dose of study drug in Part A. The Safety Set will be used for all safety analyses, with subjects analyzed according to the treatment they received, unless specified otherwise. In addition, the summary by the dosing groups (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.

9 STATISTICAL ANALYSIS

9.1 General Considerations

The Schedule of Assessments is provided in Appendix A. The precision standards for reporting safety variables are provided in an internal Biometrics document that specifies the programming rules including the precision for derived variables.

All individual subject data based on All Subjects Set of the corresponding part will be presented in data listings.

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

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

ECGs, the baseline value will be defined as the average of the pretreatment measurements on Day 1.

Change (absolute change) from baseline will be calculated as postbaseline value - baseline value.

Relative change from baseline: will be calculated and presented in percentage as 100 × (postbaseline value - baseline value)/baseline value.

Treatment-emergent Period for Part A will include the time period starting from the first dose date of the study drug through 14 days after last dose of study drug. The Treatment-Emergent period will be used for safety analyses unless specified otherwise.

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

- In the derivation of baseline measurements.
- In individual subject data listings as appropriate.

Visit windowing rules: The majority of assessments are anticipated to be on schedule. Visit windowing will not add significant value to the analysis and will not be applied. Nominal visit will be used for all assessments.

Incomplete/missing data will not be imputed, unless specified otherwise.

Outliers: No formal statistical analyses will be performed to detect or remedy the presence of statistical outliers, unless specified otherwise.

Multiplicity: No multiplicity adjustment will be performed and there is no hypothesis testing.

Unless otherwise specified, the analysis will be performed using descriptive summary statistics by dosing groups (LUM 100 mg/IVA 125 mg q12h and LUM 150 mg/IVA 188 mg q12h) and overall. All summaries will be based on the Safety Set. No statistical hypothesis testing will be performed.

9.2 Background Characteristics

9.2.1 Subject Disposition

The number of subjects in the following categories will be summarized by dosing group and overall:

- All Subjects Set
- Dosed (Safety Set)

The numbers and percentages (based on the Safety Set) of subjects in the following disposition categories will be summarized by dosing group and overall

- Completed study drug treatment
- Prematurely discontinued the treatment and the reasons for discontinuations
- Completed study
- Prematurely discontinued the study and the reasons for discontinuations

A listing will be provided for subjects who discontinued treatment or who discontinued study with reasons for discontinuation.

9.2.2 Demographics and Baseline Characteristics

Demographics, medical history and baseline characteristics will be summarized overall and by dosing group based on the Safety Set.

Demographic data will include the following:

- Age at baseline
- Sex (female and male)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other)

Baseline characteristics will include the following:

- Weight (kg)
- Stature (cm)
- BMI (kg/m2)

Medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT).

9.2.3 Prior and Concomitant Medications

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

- **Prior medication:** any medication that started before initial dosing of study drug in each part, regardless of when it ended.
- **Concomitant medication:** medication continued or newly received at or after initial dosing of study drug in each part to 14 days after the last dose of study drug in the corresponding part.
- **Post-treatment medication:** medication continued or newly received after 14 days after the last dose of study drug in each 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 by 1) preferred names; 2) anatomic class (ATC) level 1, ATC level 2, and preferred names based on the Safety Set.

Summaries of medications will be based on the Safety Set.

Details for imputing missing or partial start and/or stop dates of medication are described in Appendix B.

9.2.4 Study Drug Exposure

Duration of study drug exposure is defined as follows: last dose date − first dose date + 1 day, regardless of any interruptions in dosing. If the last dose date of study drug is missing, the subject's last date from the dosing panel (excluding PK dosing) will be used for analysis purposes.

Study drug exposure will be summarized descriptively (n, mean, SD, SE, median, min, and max in days) by dosing group and overall based on Safety Set. In addition, the summary by the dosing group (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.

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

9.3 Efficacy Analysis

Not Applicable

9.4 Safety Analysis

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

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis)
- ECGs (standard 12-lead)
- Vital signs
- Pulse oximetry
- Spirometry (subjects ≥3 years age at screening)

Safety analyses will be performed by dosing group and overall. Safety analyses will be conducted for the Safety Set. Safety data will be presented in the individual subject data listings based on the All Subjects Set. Only descriptive summary statistics of safety data will be provided (i.e., no statistical hypothesis testing will be performed).

The summary by the dosing groups (LUM 100 mg/IVA 125 mg q12h and LUM 150 mg/IVA 188 mg q12h) at each part's enrollment determined by weight at the Screening Visit will be provided as the supplementary information.

9.4.1 Adverse Events

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

- **Pretreatment AE**: any AE that started before initial dosing of study drug in each part.
- **TEAE**: any AE that increased in severity or that was newly developed during the Treatment Period which is defined as being the period from initial dosing of study drug in each part to 14 days after the last dose of study drug in the corresponding part.
- **Post-treatment AE**: any AE that increased in severity or that developed after 14 days after the last dose of study drug in each part.

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

Details for imputing missing or partial start dates of adverse events are described in Appendix C.

TEAE summaries will be presented using number and percentages of subjects.

An overview of 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

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

Separate tables will be provided summarizing the number of subjects, the number of events and the number of related events for the following by SOC and PT as per EudraCT requirement:

- Treatment-emergent Serious AEs
- Treatment-emergent Non-Serious AEs

Note if an event increases in its severity, it will be reported as a separate event in the clinical database and thus may be counted more than once.

In addition, listings that contain individual subject data for all TEAEs leading to treatment interruption, TEAEs leading to treatment discontinuation, deaths, and serious AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

9.4.2 Clinical Laboratory

For laboratory measurements, the raw values and change from baseline values of the continuous hematology/coagulation and chemistry results will be summarized by dosing group and overall in SI units at each scheduled time point. 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.

The number and percentage of subjects with at least 1 potentially clinically significant (PCS) laboratory event (i.e., categorical change) during the Treatment-Emergent period will be summarized. The PCS/categorical criteria are provided in Appendix D.

Results of urinalysis will be listed in individual subject data listings only.

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

9.4.3 Electrocardiogram

For ECG measurements, a summary of raw values and change from baseline values will be provided by dosing group and overall at each scheduled time point for the following standard 12-lead ECG measurements: RR (ms), HR (bpm), PR (ms), QRS duration (ms), QT (ms), and QT corrected for HR intervals [Fridericia's correction QTcF (ms) $=QT/RR^{1/3}$]. In addition, the mean value at each time point will be plotted for QTcF.

The number and percentage of subjects with at least 1 PCS ECG event (i.e., categorical change) during the Treatment-Emergent period will be summarized. The PCS/categorical criteria are provided in Appendix D.

The number and percentage of subjects with shift changes from baseline (normal/missing, not clinically significant, and potentially clinically significant according to overall ECG evaluation) to the worst ECG evaluation during the Treatment Period will be summarized.

9.4.4 Vital Signs

For vital signs measurements, the raw values and change from baseline values will be summarized by dosing group and overall at each scheduled time point: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute).

The number and percentage of subjects with at least 1 PCS vital sign event (i.e., categorical change) during the Treatment period will be summarized. The PCS/categorical criteria are provided in Appendix D.

9.4.5 Pulse Oximetry

For the 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.

9.4.6 Ophthalmological Examinations

Ophthalmological examination findings (Screening only) will be presented as a data listing.

9.4.7 Spirometry

Spirometry data will be presented as a data listing only.

9.4.8 Physical Examination

Physical examination findings will be presented as a data listing only.

9.4.9 Other Safety Analysis

Not applicable.

10 SUMMARY OF INTERIM AND IDMC ANALYSES

10.1 Interim Analysis

No interim analysis is planned but interim analyses may take place at any time during the study if warranted by the ongoing data, and/or deemed necessary by the internal Vertex team.

10.2 IDMC Analysis

Details of the IDMC (Section 8.2 of the protocol) analysis will be provided in the IDMC Analysis Plan. There is no IDMC analysis for Part A.

11 REFERENCES

[1]Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall G, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.

12 LIST OF APPENDICES

Appendix A: Schedule of Assessments

Table 12-1 Study VX15-809-115: Part A Screening

Assessment	Screening Visit Day -28 through Day -1
Informed consent/assent	X
Demographics	X
Medical and ophthalmological history	X
Stature, 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
Spirometry[e]	X
CFTR genotype[f]	X
Serum chemistry[g]	X
Hematology[g]	X
Coagulation studies[g]	X
Urinalysis[g]	X
Medications review[h]	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; *CFTR*: *cystic fibrosis transmembrane conductance regulator* gene; ECG: electrocardiogram; ICF: informed consent form.

[a] If children can stand unassisted and follow directions, stature should be measured as height; otherwise, stature will be measured as length. Stature and weight must be measured with shoes off and while wearing light clothing. BMI will be derived from this assessment. Refer to Section 11.4.3 of the protocol for details.

[b] The subject should rest for at least 5 minutes before having vital signs and pulse oximetry measured. Refer to Section 11.6.4 of the protocol for details.

[c] An ophthalmologic examination will be conducted by a licensed ophthalmologist. The examination does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the Screening Visit. Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination. Refer to Section 11.6.6 of the protocol for details.

[d] A standard 12-lead ECG will be performed. The subject will be instructed to rest in the supine position 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. Refer to Section 11.6.5 of the protocol for details.

[e] Spirometry (subjects ≥3 years of age at screening only) may be performed pre- or post-bronchodilator. Refer to Section 11.6.7 of the protocol for details.

[f] All subjects will be tested to assess *CFTR* genotype, regardless of availability of a previous *CFTR* genotype laboratory report. Refer to Section 11.6.2 of the protocol for details.

[g] Refer to Section 11.6.2 of the protocol for details.

[h] Refer to Section 9.4.2 of the protocol for details.

Table 12-2 Study VX15-809-115: 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)	Safety Follow-up Visit 10 (± 3) Days After the Last Dose of Study Drug
Clinic visit	X		X	X	X
Telephone contact[b]		X			
Safety Assessments					
Stature and weight[c]	X			X	X
Vital signs[d]	X		X	X	X
Pulse oximetry[d]	X		X	X	X
Full physical examination[e]	X			X	X
Standard 12-lead ECG[f]	X[g]			X[g]	X
Spirometry[h]	X		X	X	X
Serum chemistry[i]	X		X[j] (LFT only)	X	X
Hematology[i]	X			X	X
Coagulation studies[i]	X			X	X
Urinalysis[i]	X			X	X

[a] All assessments will be performed before LUM/IVA dosing unless noted otherwise (Section 11.1 of the protocol). When repeats of an assessment are required postdose at a given visit, the assessment will be collected only once 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] If children can stand unassisted and follow directions, stature should be measured as height; otherwise, stature will be measured as length. Stature and weight must be measured with shoes off and while wearing light clothing. BMI will be derived from this assessment. Refer to Section 11.4.3 of the protocol for details.

[d] The subject should rest for at least 5 minutes before having vital signs and pulse oximetry measured. Refer to Section 11.6.4 of the protocol for details.

[e] Symptom-directed physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator. Refer to Section 11.6.4 of the protocol for details.

[f] A standard 12-lead ECG will be performed. The subject will be instructed to rest in the supine position 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. Refer to Section 11.6.5 of the protocol for details.

[g] Standard 12-lead ECGs will be performed at the following times: at the Day 1 and Day 15 Visits before the morning dose of LUM/IVA, and at 1.5, 3, 4, and 6 hours after the morning dose of LUM/IVA. Predose ECGs on Day 1 will be performed in triplicate. A window of ± 15 minutes will be allowed around the nominal times for all postdose ECG assessments.

[h] Spirometry (subjects ≥3 years of age at screening only) should be performed pre-bronchodilator. On Day 1, spirometry will be performed before the morning dose and 4 hours (± 30 minutes) after the morning dose of LUM/IVA. On Day 8 and Day 15, spirometry will be performed before the morning dose of LUM/IVA. Refer to Section 11.6.7 of the protocol for details.

[i] Refer to Section 11.6.2 of the protocol for details.

[j] Liver function testing (ALT, AST, GGT, ALP, and total bilirubin) will be performed at the Day 8 Visit. Refer to Section 11.6.2 of the protocol for details.

Table 12-2 Study VX15-809-115: 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)	Safety Follow-up Visit 10 (± 3) Days After the Last Dose of Study Drug
Observation 4 hours after the first dose	X				
Medications, treatments, and procedures review[k]	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[l]		X[m]	X[n]	
Study Drug Administration					
LUM/IVA dosing[o]	**LUM/IVA q12h Day 1 through Day 15 (morning dose only on Day 15)**				

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CF: cystic fibrosis; ECG: electrocardiogram; GGT: gamma glutamyl transpeptidase; ICF: informed consent form; IVA: ivacaftor; LFT: liver function testing; LUM: lumacaftor; PK: pharmacokinetic; q12h: every 12 hours

k Refer to Section 9.4.2 of the protocol for details.
l On Day 1, a PK blood sample will be collected at 3 to 4 hours after the morning dose of LUM/IVA. Refer to Section 11.3.1 of the protocol for details.
m On Day 8, PK blood samples will be collected predose (within 60 minutes before the morning dose). Refer to Section 11.3.1 of the protocol for details.
n 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 of LUM/IVA. Refer to Section 11.3.1 of the protocol for details.
o 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 10.2.1 of the protocol. The morning dose on Day 15 is the last dose of LUM/IVA.

Appendix B: Imputation Rules for Missing Prior/Concomitant Medication Dates

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date.
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last day of the month.
    b. If DAY and Month are both missing, use the last day of the year.
    c. If DAY, Month and year are all missing, assign 'continuing' status to stop date.

In summary, the prior, concomitant or post categorization of a medication is described below.

Table 12-3 Prior, Concomitant, and Post Categorization of a Medication

	Medication Stop Date		
Medication Start Date	**< First Dose Date of Study Drug**	**≥ First Dose Date and ≤ End Date of Treatment-emergent Period**	**> End Date of Treatment-emergent Period**
< First dose date of study drug	P	PC	PCA
≥ First dose date and ≤ End date of Treatment-emergent period	-	C	CA
> End date of Treatment-emergent period	-	-	A

A: Post; C: Concomitant; P: Prior

Appendix C: Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined below:

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date; otherwise, impute the AE start day as 1.
- Otherwise, impute the AE start day as 1.

Compare the imputed AE start date with Treatment-Emergent period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date; otherwise, impute the AE start Month as January and the Day as 1.
- Otherwise, impute the AE start MONTH as January and the DAY as 1.

Compare the imputed AE start date with Treatment-Emergent period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site with no imputation. Also compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date then the AE should be considered as a pretreatment AE. Otherwise, the AE will be considered as TEAE.

Appendix D: Criteria for Potentially Clinically Significant Events

Table 12-4 Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	PCS	Comments
Clinical Chemistry		
ALT	≤3xULN*(Not a PCS criterion) >3x - ≤ 5xULN >5x - ≤ 8xULN >3xULN >5xULN >8xULN	FDA DILI Guidance Jul 2009.
AST	≤3xULN*(Not a PCS criterion) >3x - ≤ 5xULN >5x - ≤ 8xULN >3xULN >5xULN >8xULN	FDA DILI Guidance Jul 2009.
ALT or AST	ALT>3xULN or AST>3xULN	Vertex LFT working group 2014
Alkaline Phosphatase	>1.5xULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>1.5x - ≤2xULN >2xULN	FDA DILI Guidance Jul 2009.
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009. To be counted within a same treatment phase, whatever the interval between measurements.
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009. To be counted within a same treatment phase, whatever the interval between measurements.
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	Vertex LFT working group 2014
CPK	>3x - ≤ 10xULN >10xULN	FDA criteria Feb 2005. Am J Cardiol April 2006.
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<85 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥150 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.

Table 12-4 Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	PCS	Comments
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.
Albumin	≤25 g/L	
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

Table 12-5 Criteria for Potentially Clinically Significant ECGs

Parameter	PCS	Comments
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms	

Table 12-5 Criteria for Potentially Clinically Significant ECGs

Parameter	PCS	Comments
QTc Borderline Prolonged* Additional	Absolute values (ms) Borderline: 431-450 ms (Male); 451-470 ms (Female) Prolonged: >450 ms (Male); >470 ms (Female) ≥500 ms Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula.

Note: Based on CPMP 1997 guideline.

Table 12-6 Criteria for Potentially Clinically Significant Vital Signs

Parameter	PCS	Comments
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA criteria Feb 2007.

Appendix E: Details of Statistical Methodology

Percent predicted values will be calculated for parameters of FEV_1, FVC, FEV1/FVC, and $FEF_{25\%-75\%}$ using the Quanjer GLI-2012 Regression Equations and Lookup Tables.

The regression equations and lookup tables required to implement the Quanjer GLI-2012 predicted values are available in:

Quanjer GLI-2012 Regression Equations and Lookup Tables. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 7 April 2013. Available at: http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/quanjer-gli-2012-regression-equations-and-lookup-tables.aspx. Accessed 08 December 2015.

The instructions and tools on how to implement the Quanjer GLI-2012 equations are:

Implementing GLI-2012 regression equations. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 19 July 2015. Available at: http://www.ers-education.org/guidelines/global-lung-function-initiative/gli-2012-explained.aspx. Accessed 08 December 2015.

GLI-2012 - SAS Macro. Sanja Stanojevic. Version 2, 7 April 2013. Available at: http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/sas-macro.aspx. Accessed 08 December 2015.

1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number: VX15-809-115 (Final Analysis - Part B)

A Phase 3, 2-Part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation.

Author of SAP: [redacted]

Version: 2.0
Version Date of SAP: 07 September 2017

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2 TABLE OF CONTENTS

4 INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis of study VX15-809-115 Part B only and is based on the

- approved clinical study protocol, dated 13 April 2017, Version 3.0,
- approved eCRF, dated 16 December 2016, Version 4.0.

Study VX15-809-115 is a phase 3, 2-part, open-label study to evaluate the safety and pharmacokinetics (PK) of lumacaftor/ivacaftor combination therapy in subjects aged 2 through 5 years with cystic fibrosis, homozygous for the *F508del-CFTR* mutation.

This SAP (Methods) documents the planned final safety and pharmacodynamics analysis and data presentation for Part B of VX15-809-115.

SAS® Version 9.3 Software (SAS Institute, Cary, North Carolina, USA) or higher will be used to generate all statistical outputs (tables, figures, listings and datasets).

The SAP will be finalized and approved before the database lock for the final analysis for Part B. Any changes made to the SAP Methods after the above end of Part B activity has occurred will be documented in the clinical study report.
The analysis addressing the PK objective of the study will be described in the Clinical Pharmacology Analysis Plan (CPAP), which will be developed separately by the Clinical Pharmacology department at Vertex Pharmaceuticals Incorporated (Vertex).

5 STUDY OBJECTIVES

5.1 Primary Objective

Part A

To evaluate the PK of lumacaftor (LUM) and ivacaftor (IVA) and their respective metabolites in subjects aged 2 through 5 years with cystic fibrosis (CF), homozygous for *F508del*

Part B

To evaluate the safety of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for *F508del*

5.2 Secondary Objectives

Part A

To evaluate the safety of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for *F508del*

Part B

- To evaluate the pharmacodynamics (PD) of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for *F508del*
- To evaluate the off-drug PD response after the Washout Period
- To evaluate the PK of LUM and IVA and their respective metabolites in subjects aged 2 through 5 years with CF, homozygous for *F508del*

5.3 Other Objectives

Not Applicable

6 STUDY ENDPOINTS

6.1 Primary Endpoint

Part A

PK parameters of LUM and IVA

Part B

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

6.2 Secondary Endpoints

Part A

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

Part B

- Absolute change from baseline in sweat chloride at Week 24
- Absolute change from baseline in body mass index (BMI) and BMI-for-age z-score at Week 24
- Absolute change from baseline in weight and weight-for-age z-score at Week 24
- Absolute change from baseline in stature and stature-for-age z-score at Week 24
- Time-to-first pulmonary exacerbation through Week 24
- Number of pulmonary exacerbations through Week 24
- Number of CF-related hospitalizations through Week 24

- Absolute change in fecal elastase-1 (FE-1) levels from baseline at Week 24
- Absolute change in serum levels of immunoreactive trypsinogen (IRT) from baseline through Week 24
- Change in microbiology cultures from baseline at Week 24
- Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at Week 24
- Absolute change in sweat chloride from Week 24 at Week 26
- Acceptability/palatability of LUM/IVA granules at Day 1
- Absolute change from baseline in lung clearance index $(LCI)_{2.5}$ at Week 24
- Absolute change from baseline in $LCI_{5.0}$ at Week 24
- PK parameters of LUM, IVA, and their respective metabolites

7 STUDY DESIGN

7.1 Overall Design

This is a Phase 3, 2-part, open-label, multicenter study evaluating the PK, safety, tolerability, and PD of multiple doses of LUM/IVA in subjects 2 through 5 years of age (inclusive) with CF, homozygous for *F508del*. Part A is designed to evaluate the PK of LUM and IVA and their respective metabolites and the safety of LUM/IVA combination therapy. Part B is designed to evaluate the safety and PD of LUM/IVA combination therapy and also to evaluate the PK of LUM and IVA and their respective metabolites.

Subjects who participate in Part A may participate in Part B, if they meet the eligibility criteria.

Part A

Approximately 12 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 10 subjects should complete Part A. Approximately half of the subjects should complete the study in each of the following weight groups: <14 kg and ≥14 kg at screening.

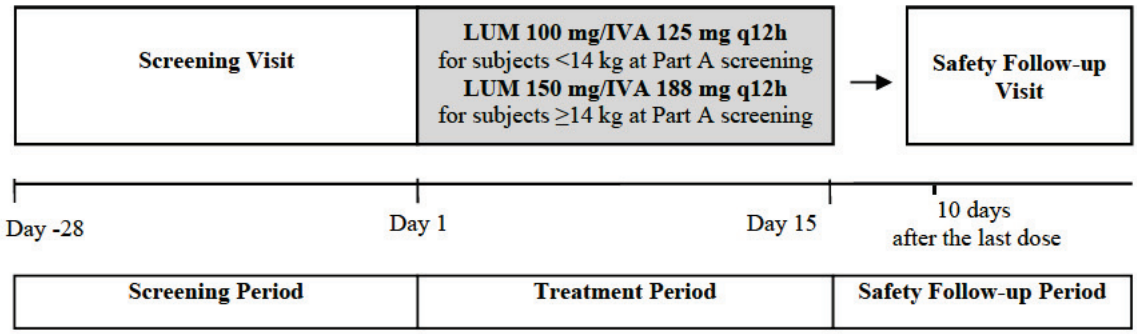
Part A includes the following:

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

Figure 7-1 depicts the schematic for the Part A study design.

A review of safety, tolerability, and available PK data will be completed by an internal Vertex team after Part A to determine the dose(s) to be evaluated in Part B. Additional subjects or treatment cohorts may be enrolled, if data from the initial, planned, 12 subjects are inadequate to make a determination of the dose(s) to be evaluated in Part B.

Figure 7-1 Schematic of Study Design for Part A



IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours
Notes: Approximately half of the subjects should complete the study in each of the following weight groups: <14 kg and ≥14 kg at screening. No dose adjustments will be made across the duration of study treatment. On Day 15, only the morning dose of LUM/IVA will be administered.

Part B

Approximately 56 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 50 subjects should complete Part B; at least 10 subjects must be <3 years of age at screening. Subjects should be ≥3 years of age at screening for enrollment in the optional LCI Substudy at a subset of sites. Additional subjects may be enrolled at the sponsor's discretion to achieve up to 30 subjects in the LCI Substudy.

Part B includes the following:

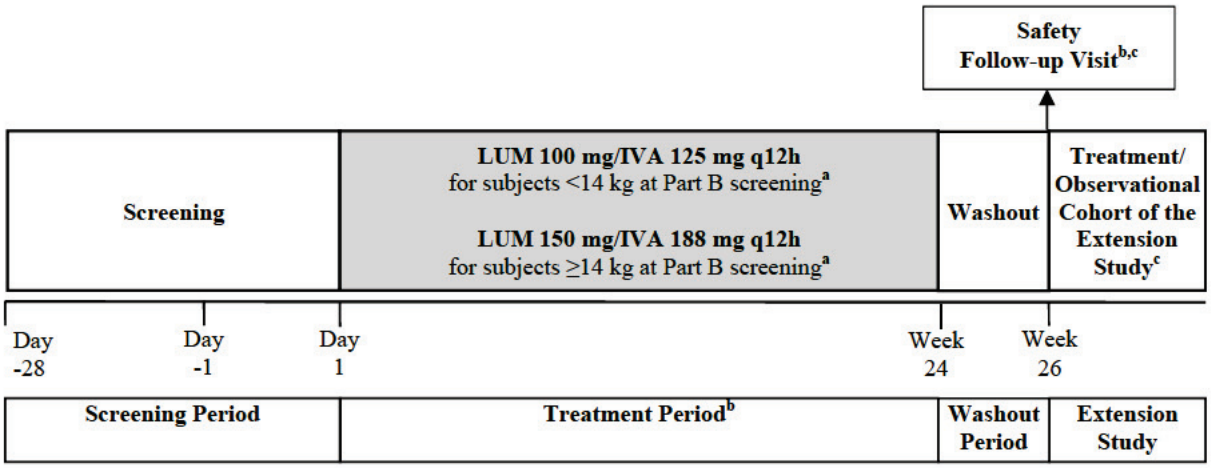
- Screening Period (Day -28 through Day -1)
- Treatment Period (Day 1 through Week 24 ± 5 days)
- Washout Period (Week 24 to Week 26 ± 4 days)
- Safety Follow up Visit (Week 26 [2 weeks ± 4 days after the last study dose of LUM/IVA])

Figure **7-2** depicts the schematic for the Part B study design.

Subjects who have completed the required visits in Part B may be eligible to enroll in the Treatment Cohort or Observational Cohort of an Extension Study to evaluate long-term treatment with LUM/IVA; enrollment will be based on the eligibility criteria. The Treatment Cohort will enroll subjects who completed LUM/IVA treatment and the Safety Follow up Visit in Part B. The Observational Cohort will enroll subjects who received at least 4 weeks of LUM/IVA treatment in Part B and completed visits up to the Safety Follow up Visit, if applicable, in Part B, but do not meet eligibility criteria for enrollment into the Treatment Cohort. 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.

In the later sections, all discussions and analyses plans will be limited to Part B only.

Figure 7-2 Schematic of Study Design for Part B



ETT: Early Termination of Treatment; IVA: ivacaftor; LCI: lung clearance index; LUM: lumacaftor; q12h: every 12 hours
Notes: Approximately 56 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 50 subjects should complete Part B; at least 10 subjects must be <3 years of age. Subjects should be ≥3 years of age for enrollment in the optional LCI Substudy at a subset of sites. Additional subjects may be enrolled at the sponsor's discretion to achieve up to 30 subjects in the LCI Substudy.

[a] The doses listed above are the planned doses for Part B. Depending on the results from Part A, a single dose from Part A may be selected for all subjects in Part B or a previously unspecified dose or doses may be selected for Part B. No dose adjustments across the duration of treatment will be made. The last dose of LUM/IVA in Part B will be the evening dose before the Week 24 Visit.

[b] Subjects who prematurely discontinue LUM/IVA treatment will be asked to complete the ETT Visit, to remain on study, and to complete the study assessments from the time of LUM/IVA discontinuation through the Week 24 Visit and the Safety Follow-up Visit, if applicable. The Safety Follow-up Visit is not required for subjects who permanently discontinue LUM/IVA treatment before or at the Week 16 Visit if they return for the Week 24 Visit or for 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 ETT Visit.

[c] Subjects who have completed the required visits in Part B may be eligible to enroll in the Treatment Cohort or Observational Cohort of an Extension Study to evaluate long-term treatment with LUM/IVA; enrollment will be based on the eligibility criteria.

Sample Size and Power

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 approximately 56 subjects are planned for enrollment and assuming a 10% dropout rate, approximately 50 subjects will complete Part B. Table 7-1 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 50 subjects (completers), there is a 92.3% chance of observing AEs in at least 1 subject if the true incidence is 5%, and a 99.5% chance of observing AEs in at least 1 subject if the true incidence is 10%. The probabilities are the binomial probabilities calculated using S-PLUS ®.

Table 7-1 Probability of Observing Adverse Events in At Least 1 Subject if the Adverse Event Incidence (θ) is 5% and 10%

Sample Size	θ = 5%	θ = 10%
50[a]	92.3%	99.5%

[a] 50 reflects the sample size of the completers.

Additional subjects may be enrolled at the sponsor's discretion to achieve up to 30 subjects in the LCI Substudy. This sample size is consistent with prior exploratory studies conducting LCI assessments.

7.2 Randomization

This is an open-label study with weight-based treatment group assignment. Randomization is not applicable.

7.3 Blinding and Unblinding

This is an open-label study. However for Part B, subjects and their legally appointed and authorized representative (e.g., parent or legal guardian) should not be informed of their study-related spirometry (subjects ≥3 years of age at screening), sweat chloride, and LCI results (subjects ≥3 years of age at screening who consent/assent to the optional LCI Substudy) during the study, regardless if the subject permanently discontinues treatment.

8 ANALYSIS SETS

8.1 All Subjects Set

All Subjects Set is defined as all subjects who have signed informed consent (and assent, if applicable) and enrolled, or dosed in Part B. This analysis set will be used for all individual subject data listings, unless specified otherwise.

8.2 Safety Set

Safety Set will include all subjects who received at least 1 dose of study drug in Part B. The Safety Set will be used for all safety analyses, with subjects analyzed according to the treatment they received, unless specified otherwise. In addition, the summary by the dosing groups (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.

8.3 Full Analysis Set

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 (except LCI) will be based on the FAS.

8.4 LCI Substudy Set

LCI Substudy Set will include all subjects who have signed informed consent (and assent, if applicable) to the optional LCI Substudy in Part B and enrolled and dosed in Part B. LCI related analysis will be based on the LCI Substudy Set.

9 STATISTICAL ANALYSIS

9.1 General Considerations

The Part B Schedule of Assessments is provided in Appendix A. The precision standards for reporting safety variables are provided in an internal Biometrics document that specifies the programming rules including the precision for derived variables.

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

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

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 Part B study drug.

For ECGs, the Part B baseline value will be defined as the average of the pretreatment measurements on Day 1.

For LCI-related parameters, the values at each visit will be calculated from the technically acceptable washout replicates. The Part B baseline of LCI will be the most recent non-missing value calculated from the technically acceptable replicates before the initial administration of study drug.

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

Change (absolute change) from baseline will be calculated as postbaseline value - Part B baseline value.

Relative change from baseline: will be calculated and presented in percentage as 100 × (postbaseline value - Part B baseline value)/ Part B baseline value.

Treatment-emergent Period for Part B will include the time period starting from the first dose date of the Part B study drug through 14 days after last dose of Part B study drug. The Treatment-Emergent period of Part B will be used for safety analyses unless specified otherwise.

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

- In scheduled visit windows per specified visit windowing rules
- In the derivation of baseline measurements/last on-treatment visit
- In the derivation of maximum/minimum values and maximum/minimum changes from baseline values
- In individual subject data listings as appropriate

Visit windowing rules: Appendix B defines the visit window mapping rules to derive the analysis visits for Part B.

Repeated observations within the same visits window:

- For all PD parameters, if there are multiple measurements within a visit window, the record at the scheduled visit will be used. If there are no measurements at the scheduled visit, then 1) the record closest to the target day will be used; or 2) if there are multiple records with the same distance to the target day, the latest record will be used.
- For all safety parameters, if there are multiple measurements within a visit window, then 1) the record closest to the target day will be used; or 2) if there are multiple records with the same distance to the target day, the latest record will be used.

BMI, weight, and stature will follow visit window rules for PD parameters when being considered as PD endpoints; they will follow visit window rules for safety parameters when being considered as safety endpoints. Their corresponding z-scores will be assigned analysis visit same as BMI, weight, and stature, respectively. Spirometry will follow the PD parameter window rule.

Incomplete/missing data will not be imputed, unless specified otherwise.

Outliers: No formal statistical analyses will be performed to detect or remedy the presence of statistical outliers, unless specified otherwise.

Multiplicity: No multiplicity adjustment will be performed and there is no hypothesis testing.

Unless otherwise specified, the analysis will be performed using descriptive summary statistics overall and by dosing groups (LUM 100 mg/IVA 125 mg q12h and LUM 150 mg/IVA 188 mg q12h). No statistical hypothesis testing will be performed.

9.2 Background Characteristics

9.2.1 Subject Disposition

The number of subjects in the following categories will be summarized overall and by dosing group:

- All Subjects Set
- Dosed (Safety Set)
- Enrolled and dosed (FAS)

The numbers and percentages (based on the Safety Set) of subjects in the following disposition categories will be summarized overall and by dosing group:

- Completed Part B study drug treatment
- Prematurely discontinued the Part B treatment
    - Reasons for discontinuations
    - Last completed scheduled on-treatment visit

- Completed Part B of study
- Prematurely discontinued the Part B of study and the reasons for discontinuations
- Rollover to extension study
    - Yes (Observational Cohort versus Treatment Cohort)
    - No

The above disposition summary will also be provided based on the LCI Substudy Set.

A listing will be provided for subjects who discontinued Part B treatment or who discontinued Part B of study with reasons for discontinuation.

9.2.2 Demographics and Baseline Characteristics

Demographics, medical history and baseline characteristics of Part B will be summarized overall and by dosing group based on the Safety Set.

Demographic data will include the following:

- Age at Part B baseline
- Age Group (< 3 and ≥ 3 years)
- Sex (female and male)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Collected per Local Regulations and Other)

Baseline characteristics will include the following:

- Weight (kg)
- Weight Group (<14 kg and ≥14 kg)
- Stature (cm)
- BMI (kg/m2)
- Weight-for-age z-score
- Stature-for-age z-score
- BMI-for-age z-score
- Sweat Chloride
- Spirometry (Subjects ≥3 years age at screening): FEV_1 (L), Percent Predicted FEV_1 (percentage points), FVC (L), Percent Predicted FVC(percentage points), $FEF_{25-75\%}$ (L/s), Percent Predicted $FEF_{25-75\%}$ (percentage points), FEV_1/FVC, Percent Predicted FEV_1/FVC (percentage points)

Similar tables for demographics and baseline characteristics will be provided based on the LCI Substudy Set. For that table, $LCI_{2.5}$ and $LCI_{5.0}$ summaries will also be summarized.

Medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT).

9.2.3 Prior and Concomitant Medications

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

- **Prior medication:** any medication that started before initial dosing of study drug in Part B, regardless of when it ended.
- **Concomitant medication:** medication continued or newly received at or after initial dosing of study drug in Part B to 14 days after the last dose of study drug in Part B.
- **Post-treatment medication:** medication continued or newly received after 14 days after the last dose of study drug in Part B.

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 by 1) preferred names; 2) anatomic class (ATC) level 1, ATC level 2, and preferred names based on the Safety Set.

Summaries of medications will be based on the Safety Set.

Details for imputing missing or partial start and/or stop dates of medication are described in Appendix C.

9.2.4 Study Drug Exposure

Duration of Part B study drug exposure is defined as follows: Part B last dose date − Part B first dose date + 1 day, regardless of any interruptions in dosing. If the last dose date of Part B study drug is missing, the subject's last date in Part B will be used for analysis purposes.

Study drug exposure will be summarized descriptively (n, mean, SD, SE, median, min, and max in days) overall and by dosing group based on Safety Set.

Additionally, the cumulative duration of Part B 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 (>0 to ≤2 weeks, >2 to ≤4 weeks, >4 to ≤8 weeks, >8 to ≤16 weeks, >16 to ≤24 weeks, and >24 weeks).

Exposure summaries will be based on the Safety Set.

9.2.5 Study Drug Compliance

Part B study drug compliance will be assessed by calculating as follows:

100 × (1 − [total number of days of Part B study drug interruption] / [duration of Part B study drug exposure + total number of days Part B 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.

In calculating the total number of days of Part B study drug being interrupted, only the interruptions with duration of ≥3 days will be considered. An interruption with duration of < 3 days will not be considered in the calculation.

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 stick packs taken will be summarized descriptively as quantitative variables (n, mean, SD, SE, median, minimum, and maximum) overall and by dosing group based on Safety Set. The number and percentage of subjects whose compliance is <80% or ≥80% and the number and percentage of subjects whose percent of stick packs taken is <80% or ≥80% will be summarized.

9.2.6 Important Protocol Deviations

An important protocol deviation and violation (IPD) is a protocol deviation that has the potential to affect the interpretation of study results. IPD will be identified from the clinical database and/or site deviation log.

The rules for identifying important protocol deviations based on the clinical database are defined in Appendix H.

All IPDs will be presented in an individual subject data listing only.

9.3 Efficacy Analysis

Not Applicable

9.4 Safety Analysis

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

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis)
- ECGs (standard 12-lead)

- Vital signs
- Pulse oximetry
- Ophthalmological examinations
- Spirometry (Subjects ≥3 years age at screening)

Safety analyses will be performed overall and by dosing group. Safety analyses will be conducted for the Safety Set. Safety data will be presented in the individual subject data listings based on the All Subjects Set. Only descriptive summary statistics of safety data will be provided (i.e., no statistical hypothesis testing will be performed).

9.4.1 Adverse Events

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

- **Pretreatment AE**: any AE that started before initial dosing of study drug in Part B.
- **TEAE**: any AE that increased in severity or that was newly developed during the Treatment Period which is defined as being the period from initial dosing of study drug in Part B to 14 days after the last dose of study drug in Part B.
- **Post-treatment AE**: any AE that increased in severity or that developed after 14 days after the last dose of study drug in Part B.

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

Details for imputing missing or partial start dates of adverse events are described in Appendix D.

TEAE summaries will be presented using number and percentages of subjects.

An overview of 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 (≥5% at the preferred term level)

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

Separate tables will be provided summarizing the number of subjects, the number of events and the number of related events for the following by SOC and PT as per EudraCT requirement:

- Treatment-emergent Serious AEs
- Treatment-emergent Non-Serious AEs

Analysis of AEs of special interest (AESI) categories:

The following AESIs are defined:

1. Elevated Transaminases

   The AESI of elevated transaminases is defined by the AEs whose PTs fall into any of the following:

   - Alanine aminotransferase abnormal
   - Alanine aminotransferase increased
   - Aspartate aminotransferase abnormal
   - Aspartate aminotransferase increased
   - Transaminases abnormal
   - Transaminases increased
   - Liver function test abnormal
   - Liver function test increased
   - Hypertransaminasaemia
   - Hepatic enzyme increased
   - Hepatic enzyme abnormal

2. Respiratory Symptom AESI

   The respiratory symptoms AESI is defined by the AEs whose PTs fall into any of the following:

   - Chest Discomfort

- Dyspnoea
- Respiration abnormal

3. Respiratory Event AESI (including respiratory symptoms or reactive airways)

   The respiratory AESI of respiratory symptoms or reactive airways is defined by the AEs whose PTs fall into any of the following:

   - Asthma
   - Bronchial hyperreactivity
   - Bronchospasm
   - Chest Discomfort
   - Dyspnoea
   - Respiration abnormal
   - Wheezing

Treatment-emergent AESIs will also be summarized

1. Showing number and percentage of subjects by PT;
2. Showing number and percentage of subjects by maximum severity;
3. Summary of duration of events (days) with descriptive statistics;
4. Summary of time-to-onset of the first event in days (relative to first dose date).
5. Showing number and percentage of subjects with TEAE leading to treatment discontinuation; with TEAE leading to treatment interruption; with serious TEAEs; with related serious TEAEs; and with TEAE leading to death.

In addition, listings that contain individual subject data for all TEAEs leading to treatment interruption, TEAEs leading to treatment discontinuation, deaths, and serious AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

9.4.2 Clinical Laboratory

For laboratory measurements, the raw values and change from Part B baseline values of the continuous hematology/coagulation and chemistry results will be summarized overall and by dosing group in SI units at each scheduled time point. 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.

The number and percentage of subjects with at least 1 categorical change during the Part B Treatment-Emergent period will be summarized. The categorical criteria are provided in Appendix E.

For each of the LFTs, mean (±SD) will be plotted at each timepoint.

Results of urinalysis will be listed in individual subject data listings only.

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

9.4.3 Electrocardiogram

For ECG measurements, a summary of raw values and change from Part B baseline values will be provided overall and by dosing group at each scheduled time point for the following standard 12-lead ECG measurements: RR (ms), HR (bpm), PR (ms), QRS duration (ms), QT (ms), and QT corrected for HR intervals [Fridericia's correction QTcF (ms) =$QT/RR^{1/3}$]. In addition, the mean value at each time point will be plotted for QTcF.

The number and percentage of subjects with at least 1 categorical change during the Part B Treatment-Emergent period will be summarized. The categorical criteria are provided in Appendix E.

The number and percentage of subjects with shift changes from baseline (normal/missing, not clinically significant, and potentially clinically significant according to overall ECG evaluation) to the worst ECG evaluation during the Treatment Period will be summarized.

9.4.4 Vital Signs

For vital signs measurements, the raw values and change from Part B baseline values will be summarized overall and by dosing group at each scheduled time point: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute).

In addition, respiratiory rate at each predose and the corresponding postdose timepoints will be summarized (1 hour, 2 hours, 4 hours, worse value of 1, 2 or 4 hours), absolute change from predose to the corresponding postdose (1 hour, 2 hours, 4 hours, worse value of 1, 2 or 4 hours) will also be summarized.

The number and percentage of subjects with at least 1 categorical change during the Treatment period will be summarized. The categorical criteria are provided in Appendix E.

Potentially abnormal SBP and DBP by their percentiles adjusted for sex, age and stature will be provided, including

- Number and percentage of subjects with categories ≥90%-<95%, ≥95%-<99% + 5 mmHg and ≥99% + 5 mmHg)
- Number and percentage of subjects with SBP and DBP percentiles ≥95% once and twice during the treatment-emergent period will be provided.
- Number and percentage of subjects with SBP and DBP percentiles ≥95% at each visit will also be provided.

The stature adjustment will be based on stature-for-age z-scores and their corresponding percentiles using the standard normal distribution (Appendix G). The stature percentiles will be further mapped per the following rules:

Table 9-1 Grouped Percentiles for stature-for-age Z-scores

Calculated Percentiles (%)	Grouped Percentiles (%)
0 – <7.5	5
7.5 – <17.5	10
17.5 – <37.5	25
37.5 – <62.5	50
62.5 – <82.5	75
82.5 – <92.5	90
92.5 – 100	95

The sex and age-adjusted normal range for SBP and DBP for each grouped stature percentiles is based on the SBP/DBP table in the National Heart, Lung, and Blood Institute (NHLBI) website (http://www.nhlbi.nih.gov/health-pro/guidelines/current/hypertension-pediatric-jnc-4/blood-pressure-tables).

9.4.5 Pulse Oximetry

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

In addition, oxygen saturation at each predose and the corresponding postdose timepoints will be summarized (1 hour, 2 hours, 4 hours, worse value of 1, 2 or 4 hours), absolute change from predose to the corresponding postdose (1 hour, 2 hours, 4 hours, worse value of 1, 2 or 4 hours) will also be summarized.

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

9.4.6 Ophthalmological Examinations

Ophthalmological examination findings will be presented as a data listing.

9.4.7 Spirometry

Spirometry data will be summarized descriptively at each visit.

The following parameters of forced expiratory volume in 1 second (FEV_1 (L)) and percent predicted FEV_1 ($ppFEV_1$), forced vital capacity (FVC) (L) and percent predicted FVC (ppFVC), FEV_1/FVC (ratio) and $ppFEV_1$/FVC as well as forced expiratory flow ($FEF_{25\%-75\%}$) (L/s) and percent predicted FEF ($ppFEF_{25\%-75\%}$) will be summarized using descriptive statistics[1]. The percent predicted values $ppFEV_1$, ppFVC, $ppFEV_1$/FVC and $ppFEF_{25\%-75\%}$ will be calculated using the standards of Global Lungs Initiative (GLI) as described in

Appendix F. In addition, the mean value (95% CI) at each time point will be plotted for the absolute change from Part B baseline in $ppFEV_1$.

In addition, ppFEV1 at each predose and the corresponding postdose timepoints will be summarized (2 hours, 4 hours, worse value of 2 or 4 hours), absolute change from predose to the corresponding postdose (2 hours, 4 hours, worse value of 2 or 4 hours) will also be summarized.

In addition, a listing containing individual subject data will be provided.

9.4.8 Physical Examination

Physical examination findings will be presented as a data listing only.

9.4.9 Other Safety Analysis

Not applicable.

9.5 Pharmacodynamic Analysis

PD analyses (except LCI) will be based on the FAS. LCI related analysis will be based on the LCI Substudy Set.

9.5.1 Analysis of Primary Endpoints

Not applicable.

9.5.2 Analysis of Secondary Pharmacodynamic Endpoints

9.5.2.1 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., a sample volume of 15 µL is required for testing and therefore any samples with volumes <15 µL will not be included in the analysis). 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. Any sweat chloride values outside of the reportable range (i.e. <10 mmol/L or >160 mmol/L) will not be included in the analysis. If a subject has replicated measurements at a postbaseline time point, then the median of the values will be used in data analyses.

Descriptive summary statistics (n, mean, SD, SE, median, minimum, and maximum), along with the 95% confidence interval 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% confidence interval and within-group *P* values based on Normal approximation, will be provided for all other visits. Mean (95% CI) at each visit, overall and by dosing groups will be plotted.

9.5.2.2 Absolute Change From Baseline in BMI/BMI-for-Age Z-score at Week 24

BMI z-score will be calculated by using Centers for Disease Control and Prevention (CDC) growth charts. The BMI z-score will be calculated as follows:

$$z = \begin{cases} \dfrac{\left(\dfrac{X}{M}\right)^{L} - 1}{LS}, & L \neq 0 \\ \dfrac{\ln\left(\dfrac{X}{M}\right)}{S}, & L = 0 \end{cases}$$

Where X is the derived BMI value in kg/m^2 based on the raw weight and raw height and L, M, and S are selected from the CDC BMI-for-age chart by subject sex and age. The BMIAGE file contains these parameters by sex (1=male, 2=female) and age; it is available at: http://www.cdc.gov/growthcharts/percentile_data_files.htm. Additionally, SAS code for calculating percentiles and z-scores is available at: http://www.cdc.gov/growthcharts/computer_programs.htm.

NOTE: The CDC BMI-for-age charts are designed for use in pediatric populations (2 to 20 years of age).

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

In addition, descriptive summary statistics, along with 95% confidence interval and within-group P values based on Normal approximation, will be provided at all other visits. Mean (95% CI) at each visit, overall and by dosing groups will be plotted.

9.5.2.3 Absolute Change From Baseline in Weight/Weight-for-Age Z-Score at Week 24

The calculation of weight z-score is similar to that of BMI z-score (using the CDC growth charts and the derivation described above). Using the same equation above, X in the equation is the collected weight and L, M, and S parameters are selected from the CDC weight-for-age chart. The WTAGE file contains these parameters by sex and age; it is available at the website http://www.cdc.gov/growthcharts/percentile_data_files.htm.

NOTE: The CDC growth charts are designed for use in pediatric populations (2 to 20 years of age).

Descriptive summary statistics (n, mean, SD, SE, median, minimum, and maximum), along with 95% confidence interval and within-group P values based on Normal approximation, will be provided for absolute change from baseline in weight and weight-for-age z-score at Week 24.

In addition, descriptive summary statistics, along with 95% confidence interval and within-group *P* values based on Normal approximation, will be provided at all other visits. Mean (95% CI) at each visit, overall and by dosing groups will be plotted.

9.5.2.4 Absolute Change From Baseline in Stature/Stature-for-Age Z-score at Week 24

The calculation of stature z-score is similar to that of BMI z-score (using the CDC growth charts and the derivation described above). Using the same equation above, *X* in the equation is the collected stature and *L*, *M*, and *S* parameters are selected from the CDC stature -for-age chart. The STATAGE file contains these parameters by sex and age; it is available at the website http://www.cdc.gov/growthcharts/percentile_data_files.htm.

NOTE: The CDC growth charts are designed for use in pediatric populations (2 to 20 years of age).

Descriptive summary statistics (n, mean, SD, SE, median, minimum, and maximum), along with 95% confidence interval and within-group *P* values based on Normal approximation, will be provided for absolute change from baseline in stature and stature-for-age z-score at Week 24.

In addition, descriptive summary statistics, along with 95% confidence interval and within-group *P* values based on Normal approximation, will be provided at all other visits. Mean (95% CI) at each visit, overall and by dosing groups will be plotted.

9.5.2.5 Analysis of Pulmonary Exacerbation-related Other Secondary Pharmacodynamic Variables

- **Time-to-first pulmonary exacerbation through Week 24:** Time-to-first pulmonary exacerbation will be analyzed using Kaplan-Meier method. Cumulative incidence of pulmonary exacerbation will be summarized and plotted. Subjects without an exacerbation by Week 24 Visit will be censored at Week 24 Visit or at the last visit before the Safety Follow-up Visit for subjects with missing Week 24 Visit.
- **Number of pulmonary exacerbations through Week 24:** The number of pulmonary exacerbations through Week 24 [inclusive] (including both on-treatment events and events after treatment discontinuation), normalized by the time spent in the study (Week 24 date – first dose date +1), will be summarized. For subjects with missing Week 24 visit, the last visit before Safety Follow-up Visit will be used instead of the Week 24 date.
- **Number of CF-related hospitalizations through Week 24:** For the number of CF-related hospitalizations through Week 24 [inclusive], the analysis will be similar to the analysis of the number of pulmonary exacerbations through Week 24.

9.5.2.6 Absolute Change in FE-1 Levels From Baseline at Week 24

Descriptive summary statistics (n, mean, SD, SE, median, minimum, and maximum), along with 95% confidence interval and within-group *P* values based on Normal approximation, will be provided for absolute change from baseline in FE-1 levels at Week 24.

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

In addition, a summary of FE-1 values (<15 µg/g and >=15 µg/g) shift from baseline to Week 24 will be displayed. A spaghetti plot of the FE-1 values will also be plotted.

Number and percentage of subjects with pancreatic insufficiency, defined as having FE-1 level <200 µg/g, will be provided at Week 24 and at baseline. The within-group shift will be tested based on McNemar's test.

9.5.2.7 Absolute Change in Serum Levels of IRT From Baseline Through Week 24

For each subject, the serum levels of IRT through Week 24 for each subject will be derived as the simple arithmetic mean at each visit (Day 15, Weeks 4, 8, 16, and 24), regardless of on-treatment measurement or measurement after treatment discontinuation. As long as there is at least 1 measurement available for a specific visit, the average of the corresponding visit will be calculated based on all available measurements. If all measurements are missing, then the average through Week 24 will be missing and the subject will not be included in the summary for the average through Week 24. The absolute change in serum levels of IRT from baseline through Week 24 will be derived similarly as the simple arithmetic mean of the absolute change in serum levels of IRT from baseline at each visit.

Summary statistics, along with 95% confidence interval and within-group *P* values based on Normal approximation, for absolute change from baseline in serum levels of IRT through Week 24 will be provided.

In additional, summary statistics, along with 95% confidence interval and within-group *P* values based on Normal approximation, will be provided at each visit.

In addition, a summary of IRT values (<14 ng/mL and >=14 ng/mL) shift from baseline to Week 24 will be displayed. A spaghetti plot of the IRT values will also be plotted.

9.5.2.8 Change in Microbiology Culture From Baseline at Week 24

The presence of bacteria will be descriptively summarized by subject counts and percentages by visit and dosing group.

9.5.2.9 Absolute Change From Baseline in ppFEV1 at Week 24

Summary statistics, along with 95% confidence interval and within-group *P* values based on Normal approximation, for absolute change from baseline in $ppFEV_1$ will be provided at Week 24 [1].

In addition, summary statistics, along with 95% confidence interval and within-group *P* values based on Normal approximation, will be provided at all other visits. Mean (95% CI) at each visit, overall and by dosing groups will be plotted.

9.5.2.10 Absolute Change in Sweat Chloride From Week 24 at Week 26

Summary statistics, along with 95% CI and within-group *P* values based on Normal approximation, for absolute change from Week 24 will be provided at Week 26.

9.5.2.11 Acceptability/Palatability of LUM/IVA Granules at Day 1

Summary statistics will be provided for the acceptability/palatability data.

9.5.2.12 Absolute Change From Baseline in LCI2.5 at Week 24

The LCI assessment at scheduled visits will be performed in multiple replicates. The LCI values at each visit included in the analysis will be the value calculated from the technically acceptable washout replicates.

When there is only one LCI value considered acceptable by the LCI central reader, the value will NOT be used. The assessment for that subject at the corresponding visit will not be included in the analysis; when there are at least 2 LCI values considered acceptable by the LCI central reader, the arithmetic mean of the values from the accepted trials will be calculated as the value at the corresponding visit.

Descriptive summary statistics (n, mean, SD, SE, median, minimum, and maximum), along with 95% confidence interval and within-group *P* values based on Normal approximation, will be provided for absolute change from baseline in $LCI_{2.5}$ at Week 24.

In addition, descriptive summary statistics, along with 95% confidence interval and within-group *P* values based on Normal approximation, will be provided at all other visits. Mean (95% CI) at each visit, overall and by dosing groups will be plotted.

9.5.2.13 Absolute Change From Baseline in LCI5.0 at Week 24

Analysis of absolute change in $LCI_{5.0}$ from baseline at Week 24 will be similar to the analysis of absolute change in $LCI_{2.5}$ from baseline at Week 24.

9.6 Narratives Listings

Narratives listings will be provided for subjects with any of the following events that occurred by the study cutoff date:

- Death
- Serious AEs
- TEAEs leading to treatment discontinuation
- LFT elevations meeting at least 1 of the following criteria:
  - ALT or AST > 5xULN, or
  - ALT>3xULN and total bilirubin>2xULN, or
  - AST>3xULN and total bilirubin>2xULN

  during the treatment-emergent period

10 SUMMARY OF INTERIM AND IDMC ANALYSES

10.1 Interim Analysis

Details of the Interim Analysis (IA) analysis will be provided in the IA/DMC Analysis Plan.

10.2 IDMC Analysis

Details of the IDMC (Section 8.2 of the protocol) analysis will be provided in the IA/DMC Analysis Plan.

11 REFERENCES

[1]Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall G, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.

12 LIST OF APPENDICES

Appendix A: Schedule of Assessments

Table 12-1 Study VX15-809-115: Part B Screening

Assessment	Screening Visit Day -28 through Day -1
Informed consent/assent	X
Demographics	X
Medical and ophthalmological history	X
Stature, 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
Coagulation studies[f]	X
Urinalysis[f]	X
Sweat chloride[g]	X
LCI (optional)[h]	X
Spirometry[i]	X
Medications review[j]	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)

BMI: body mass index; *CFTR*: *cystic fibrosis transmembrane conductance regulator* gene; ECG: electrocardiogram; ICF: informed consent form; LCI: lung clearance index

[a] If children can stand unassisted and follow directions, stature should be measured as height; otherwise, stature will be measured as length. Stature and weight must be measured with shoes off and while wearing light clothing. BMI will be derived from this assessment. Refer to Section 11.4.3 of the protocol for details.

[b] The subject should rest for at least 5 minutes before having vital signs and pulse oximetry measured. Refer to Section 11.6.4 of the protocol for details.

[c] An ophthalmologic examination will be conducted by a licensed ophthalmologist. The examination does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the Screening Visit. Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination. Refer to Section 11.6.6 of the protocol for details.

[d] A standard 12-lead ECG will be performed. The subject will be instructed to rest in the supine position 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. Refer to Section 11.6.5 of the protocol for details.

[e] All subjects will be tested to assess *CFTR* genotype, regardless of availability of a previous *CFTR* genotype laboratory report. Refer to Section 11.6.2 of the protocol for details. However, this assessment does not need to be repeated for confirmed subjects in Part A who may participate in Part B.

[f] Refer to Section 11.6.2 of the protcol for details.

[g] 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. For subjects using an historical sweat chloride value documented in their medical record to determine eligibility, the sweat chloride test at the Screening Visit is still required. At screening, 2 samples may be collected, 1 sample from each arm (left and right).

[h] The LCI assessment (subjects ≥3 years of age at screening who consent/assent to the optional LCI Substudy) may be performed pre- or post-bronchodilator. The assessment will be performed in multiple replicates and before the spirometry assessment. Refer to Section 11.4.2 of the protocol for details.

[i] Spirometry (subjects ≥3 years of age at screening only) may be performed pre- or post-bronchodilator. Refer to Section 11.6.7 of the protocol for details.

[j] Refer to Section 9.4.2 of the protocol for details.

Table 12-2 Study VX15-809-115: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period									Early Termination of Treatment (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
Telephone contact[e]		X				X		X			
Stature and weight[f]	X		X	X	X		X		X	X	X
Vital signs[g]	X[h]		X	X	X		X		X	X	X
Pulse oximetry[g]	X		X	X	X		X		X	X	X
Ophthalmologic examination									X[i]	X[i]	X[i]

[a] All assessments will be performed before LUM/IVA dosing unless noted otherwise (Section 11.1 of the protocol). When repeats of an assessment are required postdose at a given visit, the assessment will be collected only once 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, to remain on study, and to complete the study assessments from the time of LUM/IVA treatment discontinuation through the Week 24 Visit and Safety Follow-up Visit, if applicable. The ETT Visit should be scheduled as soon as possible after the subject decides to terminate LUM/IVA treatment. If the ETT Visit occurs 10 days or later following 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 subjects who permanently discontinue LUM/IVA treatment before or at the Week 16 Visit if they return for the Week 24 Visit. The Safety Follow-up Visit is not required for 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 ETT Visit.

[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 Section 8.1.2 of the protocol and 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] If children can stand unassisted and follow directions, stature should be measured as height; otherwise, stature will be measured as length. Stature and weight must be measured with shoes off and while wearing light clothing. BMI will be derived from this assessment. Refer to Section 11.4.3 of the protocol for details.

[g] The subject should rest for at least 5 minutes before having vital signs and pulse oximetry measured. Refer to Section 11.6.4 of the protocol for details.

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

[i] An ophthalmologic examination will be conducted by a licensed ophthalmologist at the Week 24 Visit OR the Safety Follow-up Visit OR the ETT Visit, as applicable. Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination. Refer to Section 11.6.6 of the protocol for details.

Table 12-2 Study VX15-809-115: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period									Early Termination of Treatment (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)		
Full physical examination[j]	X								X	X	X
Abbreviated physical examination	X[k]										
Standard 12-lead ECG[l]	X[m]		X	X	X		X		X	X	X
Serum chemistry[n]	X		X	X	X		X		X	X	X
Hematology[n]			X	X	X		X		X	X	
Coagulation studies[n]									X	X	
Urinalysis[n]	X								X	X	X
Qualitative microbiology cultures[o]	X								X		
PK sampling[p]			X	X					X		
Immunoreactive trypsinogen	X		X	X	X		X		X	X	X
Fecal elastase-1[q]	X		X	X	X		X		X	X	X
Sweat chloride[r]	X			X					X	X	X

j Symptom-directed physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator. Refer to Section 11.6.4 of the protocol for details.

k An abbreviated physical examination will be performed 4 hours (± 30 minutes) postdose on Day 1. Refer to Section 11.6.4 of the protocol for details.

l A standard 12-lead ECG will be performed. The subject will be instructed to rest in the supine position 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. Refer to Section 11.6.5 of the protocol for details.

m Standard 12-lead ECGs will be performed predose and at 4 hours (± 15 minutes) postdose on Day 1. Predose ECGs on Day 1 will be performed in triplicate.

n Refer to Section 11.6.2 of the protocol for details.

o Refer to Section 11.4.7 of the protocol for details.

p 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 after the morning dose. At the Week 24 Visit, PK blood samples will be collected at the same time as other blood collections. Refer to Section 11.3.1 of the protocol for details.

q Samples will be collected at the study center during the study visit; however, samples may be collected by the subject's caregiver up to 24 hours before the study visit (e.g., at home) and brought to the study visit (Section 11.4.5 of the protocol). The sample may be collected pre- or postdose.

r The sweat chloride test must be conducted predose relative to the morning dose of LUM/IVA during the Treatment Period (at approximately the same time as predose blood collections). At each time point, 2 samples will be collected, 1 sample from each arm (left and right). Refer to Section 11.4.1 of the protocol for details.

Table 12-2 Study VX15-809-115: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period									Early Termination of Treatment (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)		
LCI (optional)[s]	X			X					X	X	X
Spirometry[t]	X[u]		X	X	X		X		X	X	X
Other events related to outcome[v]	X		X	X	X	X	X	X	X	X	
LUM/IVA dosing[w]	LUM/IVA q12h										
Observation 4 hours after the first dose	X										
Acceptability/palatability assessment[x]	X										
Study drug count			X	X	X		X		X	X	
Medications, treatments, and procedures review[y]	Continuous from signing of ICF through Safety Follow-up Visit (if required)										
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit (if required)										

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

[s] The LCI assessment (subjects ≥3 years of age at screening who consent/assent to the optional LCI Substudy) should be performed pre-bronchodilator and before LUM/IVA dosing (Section 11.4.2 of the protocol). The assessment will be performed in multiple replicates and before the spirometry assessment.

[t] Spirometry (subjects ≥3 years of age at screening only) should be performed pre-bronchodilator. Refer to Section 11.6.7 of the protocol for details.

[u] Day 1 spirometry will be performed before LUM/IVA dosing and at 2 hours (± 30 minutes) and 4 hours (± 30 minutes) postdose.

[v] Other events related to outcome include assessments relating to pulmonary exacerbations, administration of antibiotic therapy for sinopulmonary signs or symptoms, and hospitalizations (Section 11.4.4 of the protocol).

[w] 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 (Section10.2 of the protocol). On days of scheduled visits, the morning dose of LUM/IVA will be administered at the site after predose assessments have been completed. At the Week 24 Visit, the morning dose of LUM/IVA will NOT be administered. The last dose of LUM/IVA in Part B will be the evening dose administered the day before the Week 24 Visit.

[x] Refer to Section 11.4.9 of the protocol for details.

[y] Refer to Section 9.4.2 of the protocol for details.

Appendix B: Analysis Visit Window Mapping Rules for Safety and Pharmacodynamic Measurements

Table 12-3 Visit Window Mapping Rules for Safety and Pharmacodynamic Measurements

Assessments	Visit	Target Study Day	Visit Window (in study days)
• Spirometry	Day 15	15	(1, 22]
• Weight and stature	Week 4	29	[23, 43]
• Labs	Week 8	57	[44, 85]
○ Chemistry	Week 16	113	[86, 141]
○ Hematology	Week 24	169	[142, 176]
• Vital signs			
• Pulse oximetry			
• Standard digital ECG			
• Fecal elastase -1			
• Immunoreactive trypsinogen			
• Labs	Week 24	169	(1, 176]
○ Coagulation			
• Ophthalmologic exam			
• Sweat chloride	Week 4	29	(1, 99]
• LCI	Week 24	169	[100, 176]

Special handling for Spirometry (for the change from predose to postdose analysis only):
For the change from predose to postdose spirometry analysis only, no windowing rules are used.

1. Predose spirometry: analysis visit = nominal visit;
2. Postdose 2-hour/4-hour spirometry: analysis visit = nominal visit.

Special handling for VS/ECG (for the change from predose to postdose analysis only):
For the change from predose to postdose VS/ECG analysis only, no windowing rules are used.

1. Day 1 predose VS/ECG: analysis visit = nominal visit for Day 1, Predose.
2. Day 1 post-dose VS/ECG by hour: analysis visit = nominal visit.

Special handling for Follow-up:
Follow-up will use the nominal visit and will not follow the visit window rule.

Appendix C: Imputation Rules for Missing Prior/Concomitant Medication Dates

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date.
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last day of the month.
    b. If DAY and Month are both missing, use the last day of the year.
    c. If DAY, Month and year are all missing, assign 'continuing' status to stop date.

In summary, the prior, concomitant or post categorization of a medication is described below.

Table 12-4 Prior, Concomitant, and Post Categorization of a Medication

	Medication Stop Date		
Medication Start Date	**< First Dose Date of Study Drug**	**≥ First Dose Date and ≤ End Date of Treatment-emergent Period**	**> End Date of Treatment-emergent Period**
< First dose date of study drug	P	PC	PCA
≥ First dose date and ≤ End date of Treatment-emergent period	-	C	CA
> End date of Treatment-emergent period	-	-	A

A: Post; C: Concomitant; P: Prior

Appendix D: Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined below:

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date; otherwise, impute the AE start day as 1.
- Otherwise, impute the AE start day as 1.

Compare the imputed AE start date with Treatment-Emergent period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date; otherwise, impute the AE start Month as January and the Day as 1.
- Otherwise, impute the AE start MONTH as January and the DAY as 1.

Compare the imputed AE start date with Treatment-Emergent period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site with no imputation. Also compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date then the AE should be considered as a pretreatment AE. Otherwise, the AE will be considered as TEAE.

Appendix E: Criteria for Potentially Clinically Significant Events

Table 12-5 Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	Categorical change	Comments
Clinical Chemistry		
ALT	≤3xULN*(Not a categorical change) >3x - ≤ 5xULN >5x - ≤ 8xULN >3xULN >5xULN >8xULN	FDA DILI Guidance Jul 2009.
AST	≤3xULN*(Not a categorical change) >3x - ≤ 5xULN >5x - ≤ 8xULN >3xULN >5xULN >8xULN	FDA DILI Guidance Jul 2009.
ALT or AST	ALT>3xULN or AST>3xULN	Vertex LFT working group 2014
ALT or AST	ALT>5xULN or AST>5xULN	
ALT or AST	ALT>8xULN or AST>8xULN	
Alkaline Phosphatase	>1.5xULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>1.5x - ≤2xULN >2xULN	FDA DILI Guidance Jul 2009.
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009. To be counted within a same treatment phase, whatever the interval between measurements.
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009. To be counted within a same treatment phase, whatever the interval between measurements.
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	Vertex LFT working group 2014
CPK	>3x - ≤ 10xULN >10xULN	FDA criteria Feb 2005. Am J Cardiol April 2006.
Creatinine	≥150 μmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<85 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥150 mmol/L	

Table 12-5 Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	Categorical change	Comments
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.
Albumin	≤25 g/L	
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

Table 12-6 Criteria for Potentially Clinically Significant ECGs

Parameter	Categorical change	Comments
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm <40 bpm <50 bpm >90 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	

Table 12-6 Criteria for Potentially Clinically Significant ECGs

Parameter	Categorical change	Comments
QRS	≥120 ms	
QTc Borderline Prolonged* Additional	Absolute values (ms) Borderline: 431-450 ms (Male); 451-470 ms (Female) Prolonged: >450 ms (Male); >470 ms (Female) ≥500 ms Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula.

Note: Based on CPMP 1997 guideline.

Table 12-7 Criteria for Potentially Clinically Significant Vital Signs

Parameter	Categorical change	Comments
Pulse Rate	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA criteria Feb 2007.

Appendix F: Details of Statistical Methodology

Percent predicted values will be calculated for parameters of FEV_1, FVC, FEV1/FVC, and $FEF_{25\%-75\%}$ using the Quanjer GLI-2012 Regression Equations and Lookup Tables.

The regression equations and lookup tables required to implement the Quanjer GLI-2012 predicted values are available in:

Quanjer GLI-2012 Regression Equations and Lookup Tables. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 7 April 2013. Available at: http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/quanjer-gli-2012-regression-equations-and-lookup-tables.aspx. Accessed 08 December 2015.

The instructions and tools on how to implement the Quanjer GLI-2012 equations are:

Implementing GLI-2012 regression equations. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 19 July 2015. Available at: http://www.ers-education.org/guidelines/global-lung-function-initiative/gli-2012-explained.aspx. Accessed 08 December 2015.

GLI-2012 - SAS Macro. Sanja Stanojevic. Version 2, 7 April 2013. Available at: http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/sas-macro.aspx. Accessed 08 December 2015.

Appendix G: Blood Pressure Normal Levels for Boys and Girls by Age and Height Percentile

Blood Pressure Levels for Boys by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Blood Pressure Levels for Boys by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for boys with height percentiles given in Table 3 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

Blood Pressure Levels for Girls by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
I	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Blood Pressure Levels for Girls by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for girls with height percentiles given in Table 4 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

Appendix H: Important Protocol Deviation Programming Rules (Based on the Clinical Database)

The protocol deviations that should be considered as potential IPDs include, but are not limited to:

- Subject entered the study despite violation of an inclusion or exclusion criteria
- Subject received the wrong treatment or incorrect doses
- Subject received excluded concomitant medications
- Subject remained in study despite meeting withdrawal criteria

Occurrence of any of these events should be considered as potential IPDs, but the blinded team should categorize them as IPDs only if they have the potential to affect interpretation of study results. The team should construct rules for identifying IPDs rather than identifying individual subjects with IPDs.

Important protocol deviations before first dose

1. Inclusion criteria:
    a. I3: Subjects (males and females) will be between the ages of 2 and 5 years, inclusive, on the date of informed consent (and assent, if applicable) for the relevant study part.
    b. I4: Subjects who weigh ≥8 kg without shoes and wearing light clothing at the Screening Visit.
    c. I6: Subjects who are homozygous for *F508del* (genotype to be confirmed at the Screening Visit). If the *CFTR* screening genotype result is not received before Day -1, a previous *CFTR* genotype laboratory report may be used to establish eligibility. Note:
        - Subjects who have been enrolled and whose screening genotype does not confirm study eligibility must be discontinued from the study, as described in Protocol Section 9.5.
        - This assessment does not need to be repeated for confirmed subjects in Part A who may participate in Part B.

2. Exclusion criteria:

   a. E3: Any of the following abnormal laboratory values at the Screening Visit:

      - Hemoglobin <10 g/dL
      - ALT, AST or Total bilirubin >2× ULN
      - Abnormal renal function defined as glomerular filtration rate ≤45 mL/min/1.73 m^2 (calculated by the Bedside Schwartz equation)

   b. E5: 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.

      Programming notes:

      - Check if screening QTcF>450 msec at screening, if yes,
      - Check whether ECG was repeated 2 more times during the screening period, if no, report as important protocol deviation. If yes,
      - Check whether the average of the 3 QTcF values ≤450msec, if no, report as important protocol deviation.

   c. E6: History of solid organ or hematological transplantation.

Important protocol deviations during the treatment period

1. Compliance < 80%.
2. Prohibited medication not happened during study drug interruption period (prohibited medication treatment period overlaps with study drug treatment period)

   Programming notes:
   - Prohibited medication and study drug should not be taken at the same time/day.

3. Nominal Post dose ECGs on Day 1 or Day 15 that are collected before the dosing time on the same visit.

   Programming note:
   - If the ECG is labeled as post-dose but the actual timing is pre-dose, then it should be reported as important protocol deviation.

4. Eye exam is not completed at either Week 24 or the Safety Follow-Up Visit (Week 26).
5. Subject received the wrong treatment or incorrect doses.