VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)
For Final Analysis

Protocol Number: VX16-809-116

A Phase 3, Rollover Study to Evaluate the Safety of Long-term Treatment With Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ATC	anatomic class
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CF	cystic fibrosis
CFTR	CF transmembrane conductance regulator protein
CI	confidence interval
CRF	case report form
DMC	Data monitoring committee
ECG	electrocardiogram
eCRF	electronic CRF
ETT	early termination of treatment
F508del	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FE-1	fecal elastase-1
FEV_1	forced expiratory volume in 1 second
GLI	Global Lung Function Initiative
HR	heart rate
ICF	informed consent form
IDMC	independent data monitoring committee
IPD	important protocol deviation
IRT	immunoreactive trypsinogen
IVA	ivacaftor
LCI	lung clearance index
$LCI_{2.5}$	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value
$LCI_{5.0}$	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value
LFT	liver function test
LLN	lower limit of normal
LUM	lumacaftor
Max	maximum value
Min	minimum value
MedDRA	Medical Dictionary for Regulatory Activities
OE	ophthalmological examination
PD	pharmacodynamics(s)
PE	physical examination
$ppFEV_1$	percent predicted FEV1
PR	PR interval
PT	preferred term
q12h	every 12 hours

QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
RR	interval from the onset of 1 QRS complex to the next
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SI	SI units (International System of Units)
SOC	system organ class
TE	treatment-emergent
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WHODD	World Health Organization Drug Dictionary

4 INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis of study VX16-809-116 (Study 116) and is based on the:

- approved clinical study protocol, dated 10 October 2016, Version 1.1
- approved eCRF, dated 21 August 2017, v2.0

Study 116 is a Phase 3, rollover study to evaluate the safety of long-term treatment with lumacaftor/ivacaftor (LUM/IVA) combination therapy in subjects aged 2 years and older with CF, homozygous for *F508del* . This study consists of a Treatment Cohort and an Observational Cohort. These two cohorts will be enrolled in parallel for Study VX15-809-115 (Study 115) subjects who meet the inclusion criteria.

This SAP (Methods) documents the planned statistical methods and data presentations of final analysis for subjects who previously participated in Study 115 and enrolled in Study 116. It also documents additional analyses not prespecified in the protocol, but necessary for the scientific understanding of the drug entity.

ICON has been contracted by Vertex to perform the statistical analysis. SAS® Software (SAS Institute, Cary, North Carolina, USA) Version 9.3 or higher will be used to generate all statistical outputs (tables, figures, listings and datasets).

The SAP (Methods) for the final analysis will be finalized and approved before the final clinical database lock. Any changes made to the SAP Methods after the clinical database lock has occurred will be documented in the clinical study report for this study.

5 STUDY OBJECTIVES

5.1 Primary Objective

To evaluate the long-term safety of LUM/IVA combination therapy in subjects aged 2 years and older with CF, homozygous for *F508del*

5.2 Secondary Objective

To evaluate the pharmacodynamics (PD) of long-term LUM/IVA combination therapy in subjects aged 2 years and older with CF, homozygous for *F508del*

5.3 Other Objectives

Not Applicable

6 STUDY ENDPOINTS

6.1 Primary Endpoint

Safety and tolerability assessments based on adverse events (AEs), changes in clinical laboratory values, electrocardiograms (ECGs), vital signs, pulse oximetry, ophthalmological examinations (OEs), and spirometry.

6.2 Secondary Endpoints

The following endpoints will be analyzed using baseline values in the previous (parent) study (i.e., Study 115 Part B [Study 115B]):

- Absolute change from baseline in sweat chloride

- Absolute change from baseline in body mass index (BMI) and BMI-for-age z-score
- Absolute change from baseline in weight and weight-for-age z-score
- Absolute change from baseline in stature and stature-for-age z-score
- Time-to-first pulmonary exacerbation from baseline
- Number of pulmonary exacerbations from baseline
- Number of CF-related hospitalizations from baseline
- Absolute change from baseline in fecal elastase-1 (FE-1) levels
- Absolute change from baseline in serum levels of immunoreactive trypsinogen (IRT)
- Change from baseline in microbiology cultures
- Absolute change from baseline in lung clearance index $LCI_{2.5}$
- Absolute change from baseline in $LCI_{5.0}$

[redacted]

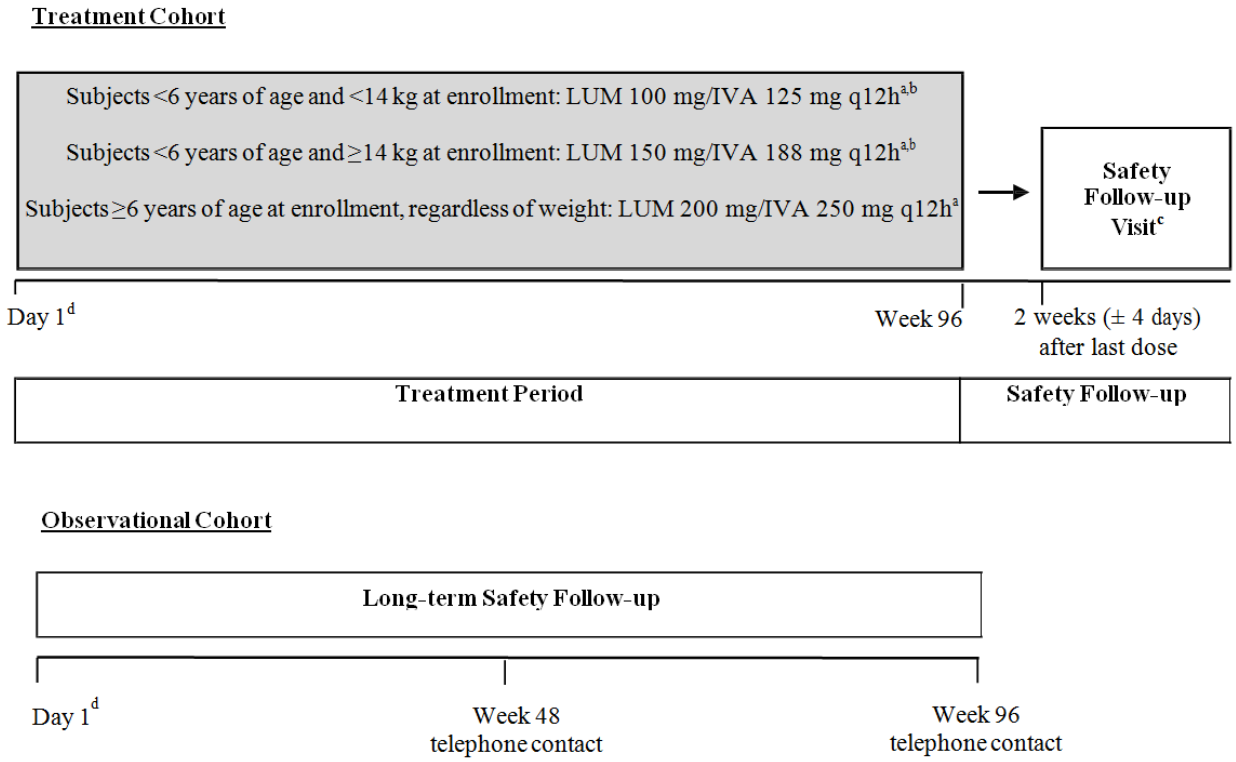
7 STUDY DESIGN

7.1 Overall Design

This is a Phase 3, open-label, multicenter study in subjects aged 2 years and older with CF who are homozygous for the *F508del-CFTR* mutation and who participated in Study 115 and meet the inclusion criteria. Study 116 is designed to evaluate the long-term safety and PD of LUM/IVA combination therapy.

This study consists of a Treatment Cohort and an Observational Cohort. These two cohorts will be enrolled in parallel as shown in Figure 7-1.

Figure 7-1 Schematic of Study Design



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

[a] Doses may be adjusted upward for changes in weight and age. See the rules for dose adjustments in Section 9.6 of the protocol.

[b] Doses are those planned for Study 115B. Based on results from Study 115A and 115B, doses for subjects <6 years of age in Study 116 may be modified.

[c] The Safety Follow-up Visit is required for 1) subjects who complete their ETT Visit <10 days after the last dose of LUM/IVA (Section 9.1.2.3 of the protocol); and 2) subjects who interrupt LUM/IVA treatment and complete their Week 96 Visit <10 days after the last dose of LUM/IVA; it is not required for subjects who continue onto commercially-available, physician-prescribed LUM/IVA within 2 weeks (± 4 days) of completing LUM/IVA treatment at the Week 96 or ETT Visit.

[d] See Section 9.1.1 of the protocol for details regarding the timing of the Day 1 Visit.

7.2 Sample Size and Power

No formal sample size calculations have been performed.

This is a long-term extension study that will enroll subjects rolled over from Study 115B.

Approximately 56 subjects were potentially eligible to be enrolled in this rollover study. Assuming a 10% dropout rate in Study 115B, 50 subjects are expected to enroll in this study.

7.3 Randomization

This is an open-label study. No randomization is planned.

Subjects in the Treatment Cohort will be treated with LUM/IVA based on their weight and age. Subjects in the Observational Cohort will not receive LUM/IVA.

7.4 Blinding and Unblinding

This is an open-label study. However, subjects and their legally appointed and authorized representative (e.g., parent or legal guardian) should not be informed of their study-related spirometry, sweat chloride, and LCI results during the study even if the subject permanently discontinued treatment.

8 ANALYSIS SETS

Enrolled subjects are those who signed informed consent/assent form and had an enrollment date on the CRF.

116 All Subjects Set is defined as all subjects who were enrolled or exposed to any amount of study drug in the Study 116 Treatment Cohort.

8.1 Efficacy Sets

Full Analysis Set (FAS): The FAS will include all subjects who were enrolled and exposed to any amount of study drug in Study 115B.

116 Full Analysis Set (116 FAS): The 116 FAS will include all subjects who were enrolled and exposed to any amount of study drug in Study 116 Treatment Cohort.

8.2 Safety Set

116 Safety Set: The 116 Safety Set will include all subjects dosed in Study 115B who are exposed to any amount of study drug in the Study 116 Treatment Cohort.

8.3 Other Analysis Set

116 LCI Substudy Set: The 116 LCI Substudy Set will include all subjects who signed informed consent/assent to the optional LCI Substudy and are enrolled and exposed to any amount of study drug in the Study 116 Treatment Cohort.

9 ANALYSIS PERIODS

9.1 Current Study Period

The **Current Study Period** starts from the first dose date of study drug in Study 116 to the last day in Study 116.

The **Treatment-Emergent Period for the Current Study Period** starts on or after the first dose date of study drug in Study 116 to 14 days (inclusive) after the last dose of study drug in Study 116 or up to the last day in Study 116, whichever occurs first.

9.2 Cumulative Study Period

The **Cumulative Study Period** starts from the first dose date of study drug in Study 115B to the last day in Study 116, regardless of

1) the planned 2-week Washout Period in Study 115B; and/or

2) the rollover gap between Study 115B and Study 116 (if any).

For subjects not enrolled in Study 116, the Cumulative Study Period will start from the first dose date of study drug in Study 115B to the last day in Study 115B.

10 STATISTICAL ANALYSIS

10.1 General Considerations

For the Treatment Cohort, all individual subject data will be presented in data listings based on the 116 All Subjects Set.

For the Observational Cohort, listings will be provided only for disposition, demographics, and serious adverse events (SAEs). Listings will be provided based on all subjects enrolled in the Observational Cohort.

Treatment Cohort

Continuous variables will be summarized using descriptive summary statistics: number of subjects, mean, standard deviation (SD), standard error (SE), median, minimum value (Min), and maximum value (Max). Precisions of the summary for continuous variables are detailed in Appendix B.

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

Baseline: The baseline value is defined as the most recent non-missing measurement (scheduled or unscheduled) before intake of the first dose of study drug in Study 115B, except specified otherwise.

- For ECGs, the baseline will be defined as the average of the pretreatment measurements on the start of Study 115B.
- For LCI-related parameters, the values at each visit will be calculated from the technically acceptable replicates. The baseline of LCI will be the most recent non-

missing value calculated from the technically acceptable replicates before the initial administration of study drug in the Study 115B.

- For sweat chloride, the values at each visit will be based on the averaged measurements from left and right arms. The baseline is defined as the average of the values at screening and the pretreatment measurement on Day 1 of Study 115B. For assessments where there is only 1 pre-first dose sweat chloride measurement available, that measurement will be considered the baseline.

Change (Absolute Change) from baseline will be calculated as

Post-baseline value – Baseline value.

Relative change from baseline will be calculated and presented in percentage as

100 × (Post-baseline value − Baseline value)/Baseline value.

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

- In scheduled visit windows per specified visit windowing rules.
- In the derivation of baseline measurements.
- In individual subject data listings as appropriate.

Visit windowing rules: Appendix C defines the visit window mapping rules to derive the analysis visits for study 116.

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 to analysis visits 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.

10.2 Background Characteristics

Treatment Cohort

10.2.1 Subject Disposition

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

- 116 All Subjects Set
- Full Analysis Set
- 116 Full Analysis Set
- 116 Safety Set
- 116 LCI Substudy Set

The number and percentages of subjects will be provided with the number in the 116 Safety Set as denominator. The number of subjects enrolled but never dosed in Study 116 will be provided without a percentage.

- Enrolled but never dosed (only showing number of subjects)
- Completed treatment
- Prematurely discontinued treatment and the reasons for discontinuations
- Last scheduled on-treatment visit completed for subjects who discontinued treatment
- Completed study (any subject who has completed the Safety Follow-up Visit)
- Prematurely discontinued the study and the reasons for discontinuations

Subjects prematurely discontinue treatment before Week 96 due to commercial drug available will be captured in the CRF pages, with primary reason for dosing ended under the "Other" category of "Discontinued" and free text to describe treatment discontinuation due to commercial drug available.

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

10.2.2 Demographics and Baseline Characteristics

Treatment Cohort

Demographics, baseline characteristics, and medical history will be summarized. Demographic data (at Study 115B baseline) will include the following:

- Age at baseline (months)
- Age Group at Baseline (< 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 at Baseline (<14 kg and ≥14 kg)
- Stature (cm)
- BMI (kg/m^2)
- Weight-for-age z-score
- Stature-for-age z-score
- BMI-for-age z-score
- Sweat Chloride
- FEV_1 (L)
- Percent predicted FEV_1 ($ppFEV_1$, percentage points)
- $LCI_{2.5}$ and $LCI_{5.0}$

Medical history will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT). All demographic and baseline characteristic data will be listed.

10.2.3 Prior and Concomitant Medications

Medications used in this study will be coded by using the World Health Organization Drug Dictionary (WHODD, March 2018, Format B3 or higher) and categorized as the following:

- **Prior medication**: any medication continued or newly received before initial dosing of study drug in Study 115B.
- **Concomitant medication**: medication continued or newly received during the Treatment-emergent Period of the Current Study Period.
- **Post-treatment medication**: medication continued or newly received after the end of the treatment-emergent Period of the Current Study Period.

A given medication can be classified as a prior medication, concomitant medication, or a post-treatment medication; both concomitant and post-treatment; both prior and concomitant; 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 more than 14 days after the last dose of study drug, it will be considered as prior, concomitant, and post-treatment.

Incidence of prior medications will be summarized based on the 116 Safety Set by 1) Preferred name; 2) Anatomic class (ATC) level 1, ATC level 2, and preferred name.

Incidence of concomitant medications will be summarized based on 116 Safety Set for Current Study Period by 1) Preferred name; 2) Anatomic class (ATC) level 1, ATC level 2, and preferred name.

All medications in the Current Study Period will be listed for each subject.

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

10.2.4 Study Drug Exposure

Study drug exposure will be summarized for the Current Study Period based on 116 Safety Set.

Duration of study drug exposure is defined as: last available dose date of the Current Study Period − first dose date of the Current Study Period + 1 day, regardless of unplanned interruptions.

Duration of study drug exposure as well as number of sticks/tablets administered defined as (total number of sticks and/or tablets dispensed) − (total number of sticks and/or tablets returned) will be summarized descriptively. Additionally, the total duration of treatment exposure, defined as the sum of the subject's duration of treatment exposure and expressed in subject-years (1 subject with 48 weeks of treatment exposure is considered 1 subject-year) will be provided.

Duration of exposure will also be summarized as a categorical variable (>0 to ≤8 weeks, >8 to ≤24 weeks, >24 to ≤48 weeks, >48 to ≤72 weeks, >72 to ≤96 weeks, >96 weeks).

10.2.5 Study Drug Compliance

Study drug compliance will be summarized for the Current Study Period based on 116 Safety Set.

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

Treatment compliance percentages will be summarized descriptively (number, mean, SD, median, minimum, and maximum). The number and percentage of subjects whose compliance is <80% or ≥80% will be also be summarized.

In calculating the total number of days of 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.

Study drug exposure and compliance data for each subject will also be listed.

10.2.6 Important Protocol Deviations

IPDs will be identified from the clinical database and/or site deviation log. Important protocol deviations will be provided as a subject data listing, indicating the source (clinical database versus site deviation log). All potential IPDs from both sources will be reviewed by the study team before the final database lock to determine IPD status.

The rules for identifying programmable IPDs based on the clinical database are defined in Appendix I.

IPDs will be provided as a subject data listing based on the 116 All Subjects Set.

10.3 Pharmacodynamic Analysis

10.3.1 Analysis of Primary Endpoints

Not applicable.

10.3.2 Analysis of Secondary Pharmacodynamic Endpoints

10.3.2.1 Absolute Change from Baseline in Sweat Chloride

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.

Raw values and absolute change from parent study baseline in sweat chloride at each visit in the Current Study Period (including all measurements from Study 116, including the Safety Follow-up Visit of Study 116, both on-treatment measurements and measurements after treatment discontinuation), will be summarized for the overall group based on 116 FAS. Descriptive statistics including number of subjects, mean, SD, SE, median, minimum, and maximum will be provided for the absolute change from parent study baseline. In addition, the 95% CI and the within-group *P* value based on Normal approximation will be provided. The mean (95% CI) of the absolute change from parent study baseline will be plotted.

10.3.2.2 Absolute Change from Baseline in BMI/BMI-for-Age Z- score

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:

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

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).

Raw values and absolute change from parent study baseline in BMI and BMI-for-age z-score at each visit in the Current Study Period will be summarized descriptively. The 95% CI based on Normal approximation will also be provided. The mean (95% CI) of the absolute change from parent study baseline will be plotted.

10.3.2.3 Absolute Change from Baseline in Weight, Weight-for-Age Z-score

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).

Weight and weight-for-age z-score will be analyzed in a similar way to BMI and BMI-for-age z-score.

10.3.2.4 Absolute Change from Baseline in stature and stature-for-age z-score

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).

Stature and stature-for-age z-score will be analyzed in a similar way to BMI and BMI-for-age z-score.

10.3.2.5 Absolute change from Baseline in $LCI_{2.5}$ and $LCI_{5.0}$

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.

$LCI_{2.5}$ and $LCI_{5.0}$ will be analyzed in a similar way to BMI and BMI-for-age z-score.

10.3.2.6 Analysis of Pulmonary Exacerbation-related Other Secondary Pharmacodynamic Variables

Time-to-first pulmonary exacerbation: Time-to-first pulmonary exacerbation, defined as days from study drug initiation in the Study 115B to first pulmonary exacerbation, will be analyzed using Kaplan-Meier (KM) method based on the FAS for the Cumulative Study Period. Cumulative incidence of pulmonary exacerbation will be summarized for the overall group. Subjects without an exacerbation will be considered censored at the end date of the Cumulative Study Period.

Number of pulmonary exacerbations: The number of pulmonary exacerbations starting during the Cumulative Study Period (including both on-treatment events and events after treatment discontinuation), normalized by the time spent in the Cumulative Study Period (last date in the Cumulative Study Period – first date in the Cumulative Study Period + 1), will be summarized for the overall group based on the FAS.

Number of CF-related hospitalizations through last visit: The number of CF-related hospitalizations occurring during the Cumulative Study Period (including both on-treatment events and events after treatment discontinuation), normalized by the time spent in the Cumulative Study Period (last date in the Cumulative Study Period – first date in the Cumulative Study Period + 1), will be summarized for the overall group based on the FAS.

10.3.2.7 Absolute Change in FE-1 Levels From Baseline

The raw values and absolute change from parent study baseline in FE-1 will be summarized at each scheduled visit during the Current Study Period for the overall group based on the 116 FAS. In addition, the number and percentage of subjects with shift changes from parent study baseline [<15 µg/g, >=15 µg/g to <200 µg/g (consistent with pancreatic insufficient), and >=200 µg/g (consistent with pancreatic sufficient)] at each visit and at any visits (<15 µg/g, >=15 µg/g to <200 µg/g, and >=200 µg/g) in the Current Study Period will be provided. A spaghetti plot of the FE-1 values will also be provided including Study 115B baseline, and visits in the Current Study Period.

10.3.2.8 Absolute Change in Serum Levels of IRT From Baseline

The raw values and absolute change from parent study baseline in IRT will be summarized at each scheduled visit during the Current Study Period for the overall group based on the 116 FAS. A spaghetti plot of the IRT values will also be provided including Study 115B baseline, and visits in the Current Study Period.

10.3.2.9 Analysis in Microbiology Cultures

The presence of bacteria will be descriptively summarized by subjects' counts and percentages. Number and percentage of subjects with microbiology cultures in each category during the Current Study Period will be summarized descriptively by visit based on the 116 FAS, for each possibly-detected organism.

[redacted]

10.4 Efficacy Analysis

Not Applicable.

10.5 Safety Analysis

Observational Cohort

Listings of SAEs will be provided based on all subjects enrolled in the Observational Cohort.

Treatment Cohort

Evaluating safety of long-term LUM/IVA treatment in the Treatment Cohort is the primary objective of this study. The overall safety profile of study drug will be assessed in terms of the following safety and tolerability endpoints:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (serum chemistry, hematology, coagulation studies and urinalysis)
- ECGs (standard 12-lead)
- Vital signs
- Pulse oximetry
- OEs
- Spirometry (subjects ≥3 years age at screening in Study 115B)

The safety analysis will be performed based on the 116 Safety Set for the Current Study Period. Only descriptive summary statistics of safety data will be provided (i.e., no statistical hypothesis testing will be performed). All listings will be provided based on the 116 All Subjects Set.

The safety summaries described in the sections below will be performed for the Treatment Cohort based on the Current Study Period only.

10.5.1 Adverse Events

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

- **TEAE:** any AE that increased in severity or that was newly developed during the Treatment-emergent Period of the Current Study Period.
- **Post-treatment AE:** any AE that increased in severity or that was newly developed after the end of the Treatment-emergent Period of the Current Study Period.

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 AEs are described in Appendix E.

TEAE summaries will be presented using number and percentages of subjects for the Current Study Period based on 116 Safety Set.

An overview of the TEAE profile will be provided, including total number of TEAEs, with number and percentage of subjects for the following categories: 1) all TEAEs; 2) Grade 3/4 TEAEs; 3) TEAEs by relationship; 4) TEAEs by maximum severity; 5) TEAEs leading to treatment interruption; 6) TEAEs leading to treatment discontinuation; 7) serious TEAEs; 8) 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 maximal 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 for the overall column)

Summaries will be presented by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects). 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.

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

Analysis of AEs of special interest (AESI):

Three categories of AESI are defined: elevated transaminases, respiratory symptom AESI and respiratory event AESI. Treatment-emergent AESIs will be summarized by

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

10.5.2 Clinical Laboratory

For the laboratory measurements, the raw values and change from parent study baseline of the continuous hematology and chemistry results will be summarized in SI units at each visit in the Current Study Period (including all measurements from Study 116) for the overall group based on the 116 Safety Set.

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 in the Current Study Period will be summarized for the overall group based on the 116 Safety Set.

The number and percentage of subjects meeting the defined threshold criteria during the Treatment-emergent Period of the Current Study Period will be provided based on the 116 Safety Set. The threshold criteria are provided in Appendix F.

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 reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

10.5.3 Electrocardiogram

For the ECG measurements, a summary of raw values and change from parent study baseline will be provided at each scheduled time point of the Current Study Period (including all measurements from Study 116) based on the 116 Safety Set for the overall group, for the following standard digital ECG measurements: RR, PR, QT, and QT corrected for HR (QTc) intervals (Fridericia's correction [$QTcF = QT/RR^{1/3}$], QRS duration, and HR. In addition, the mean value at each time point will be plotted for QTcF.

The number and percentage of subjects meeting the defined threshold criteria during the Treatment-emergent Period of the Current Study Period will be summarized based on 116 Safety Set. The threshold criteria are provided in Appendix F.

The number and percentage of subjects with shift changes from parent study baseline (normal/missing, not clinically significant, and potentially clinically significant according to overall ECG evaluation) to the worst ECG evaluation during the Treatment-emergent Period of the Current Study Period will be summarized based on 116 Safety Set.

Listings will be provided for the ECG measurements.

10.5.4 Vital Signs

For the vital signs measurements, the raw values and change from parent study baseline values will be summarized at each scheduled time point of the Current Study Period (including all measurements from Study 116) based on the 116 Safety Set: systolic and diastolic blood pressure (mm Hg), body temperature (^{o}C), pulse rate (beats per minute), respiratory rate (breaths per minute), as well as weight, stature, and BMI.

The number and percentage of subjects meeting the defined threshold criteria during the Treatment-emergent Period of the Current Study Period will be summarized based on 116 Safety Set. The threshold criteria are provided in Appendix F.

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 during the treatment-emergent period of the Current Study Period
- Number and percentage of subjects with SBP and DBP percentiles ≥95% once and twice during the treatment-emergent period of the Current Study Period
- Number and percentage of subjects with SBP and DBP percentiles ≥95% at each visit in the Current Study Period

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

Table 10-1 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). The mean value at each time point will be plotted for SBP and DBP. Listings will be provided for the vital signs parameters. Listing of subjects with potentially abnormal SBP or DBP will also be provided.

10.5.5 Pulse Oximetry

For the pulse oximetry measurements, a summary of raw values and change from parent study baseline will be provided at each scheduled time point in the Current Study Period for the percent of oxygen saturation based on the 116 Safety Set.

The number and percentage of subjects with shift changes from parent study baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the Treatment-emergent Period of the Current Study Period, will be summarized based on the 116 Safety Set.

Listings will be provided for the pulse oximetry measurements.

10.5.6 Ophthalmological Examinations

OE findings will be presented as a data listing.

10.5.7 Spirometry

Spirometry data will be summarized descriptively at each Study 116 visit based on the 116 Safety Set for subjects who are ≥3 years of age at screening in Study 115B based on 116 FAS. Spirometry measurements from subjects who turn 3 years of age during the Study 115B or Study 116 will not be included in the summary. The raw values and absolute change/relative change from parent study baseline will be summarized at each scheduled time point of the Current Study Period.

The following parameters: forced expiratory volume in 1 second (FEV_1 (L)), percent predicted FEV_1 ($ppFEV_1$), forced vital capacity (FVC (L)), percent predicted FVC (ppFVC), FEV_1/FVC 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 at each visit in the Current Study Period. The percent predicted values $ppFEV_1$, ppFVC, $ppFEV_1$/FVC and $ppFEF_{25\%-75\%}$ will be calculated using the standards of Global Lungs Initiative[1] (GLI) as described in Appendix G.

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

10.5.8 Physical Examination

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

10.5.9 Other Safety Analysis

Not Applicable

11 SUMMARY OF INTERIM AND IDMC ANALYSES

11.1 Interim Analysis

No interim analysis is planned.

11.2 IDMC Analysis

Safety and tolerability data was reviewed by the IDMC to ensure the safety of the subjects in the study based on the data cut as of 09 March 2018. Procedural details of the IDMC's structure and function and data planned for review is outlined in the IDMC charter. The statistical analysis methodology was specified in the IDMC analysis plan. DMC charter and IDMC SAP were finalized before the IDMC review meeting.

12 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.

13 LIST OF APPENDICES

Appendix A: Schedule of Assessments

Table 13-1 Study VX16-809-116: Treatment Cohort - Treatment Period and Safety Follow-up Visit

	Treatment Period					ETT Visit[b]	Safety Follow-up Visit[c]
Event/Assessment[a]	Day 1[d]	Day 3 (± 1 Day)	Day 15 (± 3 Days)	Weeks 12, 24, 36, 48, 60, 72, 84 (± 7 Days)	Week 96 (± 7 Days)	As Soon as Possible After the Last Dose	2 Weeks (± 4 Days) After the Last Dose
Informed consent/assent	X						
Clinic visit	X		X	X	X	X	X
Telephone contact[e]		X					
Stature and weight[f]	X		X	X	X	X	X
Vital signs[g]	X[h]		X	X	X	X	X
Pulse oximetry[g]	X		X	X	X	X	X
OEs[i]	X			Week 48[j]	X[j,k]	X[j,k]	X[j,k]
Full PE[l]	X			Weeks 24, 48, 72	X	X	X
Abbreviated PE	X[m]						

[a] Assessments will be performed before LUM/IVA dosing unless noted otherwise.
[b] If the ETT Visit occurs 10 days or later after the last dose of LUM/IVA, the Safety Follow-up Visit will not be required (Section 9.1.2.3 of the protocol). Subjects who prematurely discontinue LUM/IVA treatment for AEs should be followed until the AE is considered resolved.
[c] The Safety Follow-up Visit is required for 1) subjects who complete their ETT Visit <10 days after the last dose of LUM/IVA (footnote b and Section 9.1.2.3 of the protocol); and 2) subjects who interrupt LUM/IVA treatment and complete their Week 96 Visit <10 days after the last dose of LUM/IVA; it is not required for subjects who continue onto commercially-available, physician-prescribed LUM/IVA within 2 weeks (± 4 days) of completing LUM/IVA treatment at the Week 96 or ETT Visit.
[d] For subjects at sites activated by the time of their Study 115B Safety Follow-up Visit, their Study 116 Day 1 Visit will be on the same day as their Study 115B Safety Follow-up Visit, and any Study 116 Day 1 assessments that were specified to be performed at the Study 115B Safety Follow-up Visit do not need to be repeated. If the Study 116 Day 1 Visit does not coincide with the subject's Study 115B Safety Follow-up Visit, the subject will complete all Study 116 Day 1 assessments (except the OE if it was performed within the last 3 months before the visit). See Section 9.1.1 of the protocol for details.
[e] Telephone contacts will be made to assess the subject's status, any AEs, medications, treatments, and procedures.
[f] If subjects can stand unassisted and follow directions, stature should be measured as height; otherwise, stature will be measured as length. Stature and weight must be measured with shoes off and while wearing light clothing. BMI will be derived from this assessment. See 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. See 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 OE will be conducted by a licensed ophthalmologist. Subjects with documentation of bilateral lens removal do not need the OE. See Section 11.6.6 of the protocol for details.
[j] Subjects may complete the OE within ± 1 week of the scheduled visit.

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

[l] Symptom-directed PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator. See Section 11.6.4 of the protocol for details.

[m] An abbreviated PE will be performed 4 hours (± 30 minutes) postdose on Day 1. See Section 11.6.4 of the protocol for details

Table 13-1 Study VX16-809-116: Treatment Cohort - Treatment Period and Safety Follow-up Visit

	Treatment Period					ETT Visit[b]	Safety Follow-up Visit[c]
Event/Assessment[a]	Day 1[d]	Day 3 (± 1 Day)	Day 15 (± 3 Days)	Weeks 12, 24, 36, 48, 60, 72, 84 (± 7 Days)	Week 96 (± 7 Days)	As Soon as Possible After the Last Dose	2 Weeks (± 4 Days) After the Last Dose
Standard 12-lead ECGs[n]	X		X	Week 48	X	X	X
Serum chemistry[o]	X		X	Weeks 12, 24, 36, 48, 72	X	X	X
Hematology[o]				Weeks 12, 24, 36, 48, 72	X	X	X
Coagulation studies[o]				Week 48	X		
Urinalysis[o]	X			Week 48	X		
Qualitative microbiology cultures[p]	X			Weeks 24, 48, 72	X	X	
Immunoreactive trypsinogen	X			Week 48	X		X
Fecal elastase-1[q]	X			Week 48	X		X
Sweat chloride[r]	X			Weeks 24, 48	X		X
LCI (optional)[s]	X			Weeks 24, 48	X		X
Spirometry[t]	X[u]		X	Weeks 24, 48	X	X	X
Other events related to outcome[v]	X		X	X	X	X	X
LUM/IVA dosing[w]	LUM/IVA q12h						
Observation 4 hours after the first dose	X						
Study drug count	X		X	X	X	X	

[n] 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. See Section 11.6.5 of the protocol for details.

[o] See Section 11.6.2 of the protocol for details.

[p] See Section 11.4.7 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 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 will be conducted 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). See Section 11.4.1 of the protocol for details.

[s] The LCI assessment (only subjects who are ≥3 years of age at Study 115B screening who consent/assent to the optional LCI Substudy in Study 115B and Study 116) should be performed pre-bronchodilator. See Sections 11.1 and 11.4.2 of the protocol for details. The assessment will be performed in multiple replicates and before the spirometry assessment.

[t] Spirometry (only subjects who are ≥3 years of age at Study 115B screening) should be performed pre-bronchodilator. See Sections 11.1 and 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 (Section 9.6 of the protocol). On days of scheduled visits, the dose will be administered at the site after predose assessments have been completed. The last dose will be the dose administered before the Week 96 Visit. See Section 9.6 of the protocol for dose determination details.

Table 13-1 Study VX16-809-116: Treatment Cohort - Treatment Period and Safety Follow-up Visit

	Treatment Period					ETT Visit[b]	Safety Follow-up Visit[c]
Event/Assessment[a]	**Day 1[d]**	**Day 3 (± 1 Day)**	**Day 15 (± 3 Days)**	**Weeks 12, 24, 36, 48, 60, 72, 84 (± 7 Days)**	**Week 96 (± 7 Days)**	**As Soon as Possible After the Last Dose**	**2 Weeks (± 4 Days) After the Last Dose**
Medications, treatments, and procedures review	Continuous from signing of ICF through Safety Follow-up Visit (if required)						
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit (if required)						

AE: adverse event; BMI: body mass index; ECG: electrocardiogram; ETT: Early Termination of Treatment; ICF: informed consent form; IVA: ivacaftor; LCI: lung clearance
index; LUM: lumacaftor; OE: ophthalmological examination; PE: physical examination; q12h: every 12 hours

Table 13-2 Study VX16-809-116: Observational Cohort

Event/Assessment	Day 1[a]	Long-term Follow-up Telephone Contact Weeks 48 and 96 (± 4 weeks)	Early Termination Telephone Contact[b]
Informed consent/assent	X		
Clinic visit	X		
Telephone contact		X	X
Serious adverse events	Continuous from signing of ICF through Week 96 or Early Termination Telephone Contact		

ICF: informed consent form; IVA: ivacaftor; LUM: lumacaftor

a For subjects at sites activated by the time of their applicable Study 115B visit (i.e., the Week 24 Visit or the Safety Follow-up Visit, if required), their Study 116 Day 1 Visit will be the same day as their applicable Study 115B visit, and any Study 116 Day 1 assessments that were specified to be performed at the applicable Study 115B visit do not need to be repeated. If the Study 116 Day 1 Visit does not coincide with the subject's applicable Study 115B visit, the subject will complete all Study 116 Day 1 assessments. See Section 9.1.1 of the protocol for details.

b Subjects who become eligible to receive commercially-available, physician-prescribed LUM/IVA, and who choose to continue onto commercially-available LUM/IVA, must have an Early Termination Telephone Contact to terminate study participation

Appendix B: Standards for Safety and Efficacy Variable Display in TFLs

Continuous Variables

The precision for continuous variables has been specified in the Vertex Standard Programming Rules document (Version 1.0, December 2015):

[redacted]

Categorical Variables: Percentages will be presented to 1 decimal place.

Appendix C: Analysis Visit Windows for Safety and Pharmacodynamic Assessments

Table 13-3 Visit Window Mapping Rules for Safety Measurements (809-116)

Assessments	Study 116 Visit	Target Study Day	Visit Window (in study days)
• Weight and stature	116 Day 15	15	(1, 50]
• Vital signs	116 Week 12	85	[51, 127]
• Pulse oximetry	116 Week 24	169	[128, 211]
	116 Week 36	253	[212, 295]
	116 Week 48	337	[296, 379]
	116 Week 60	421	[380, 463]
	116 Week 72	505	[464, 547]
	116 Week 84	589	[548, 631]
	116 Week 96	673	[632, 680]
	116 Follow-up Visit	687	Nominal Visit
• Standard digital ECG	116 Day 15	15	(1, 176]
	116 Week 48	337	[177, 505]
	116 Week 96	673	[506, 680]
	116 Follow-up Visit	687	Nominal Visit
• Labs	116 Day 15	15	(1, 50]
○ Chemistry	116 Week 12	85	[51, 127]
	116 Week 24	169	[128, 211]
	116 Week 36	253	[212, 295]
	116 Week 48	337	[296, 421]
	116 Week 72	505	[422, 589]
	116 Week 96	673	[590, 680]
	116 Follow-up Visit	687	Nominal Visit
• Labs	116 Week 12	85	(1, 127]
○ Hematology	116 Week 24	169	[128, 211]
	116 Week 36	253	[212, 295]
	116 Week 48	337	[296, 421]
	116 Week 72	505	[422, 589]
	116 Week 96	673	[590, 680]
	116 Follow-up Visit	687	Nominal Visit
• Labs	116 Week 48	337	(1, 505]
○ Coagulation	116 Week 96	673	[506, 680]
	116 Follow-up Visit	687	Nominal Visit
• Spirometry	116 Day 15	15	(1, 92]
	116 Week 24	169	[93, 253]
	116 Week 48	337	[254, 505]
	116 Week 96	673	[506, 680]
	116 Follow-up Visit	687	Nominal Visit
• Sweat chloride	116 Week 24	169	(1, 253]
• LCI	116 Week 48	337	[254, 505]
	116 Week 96	673	[506, 680]
	116 Follow-up Visit	687	Nominal Visit

• FE-1 • IRT	116 Week 48	337	(1, 505]
	116 Week 96	673	[506, 680]
	116 Follow-up Visit	687	Nominal Visit

The study days are based on the first dose in 116.

Special handling for vitals signs and spirometry:

- Day 1 post-dose measurements by hour, assign analysis visit = nominal visit.

Appendix D: 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 13-4 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 E: 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 F: Criteria for Threshold Analysis

Table 13-5 Threshold Analysis Criteria for 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	

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 13-6 Threshold Analysis Criteria for 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	
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 13-7 Threshold Analysis Criteria for 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 G: Details of GLI Equation for Calculating ppFEV$_1$

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 I: Programmable Important Protocol Deviation Programming Rules (Based on the Clinical Database)

Important Protocol Deviations during the Treatment Period:

- Compliance < 80% in the Treatment Cohort of Study 116