1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number: VX16-809-122 (Final Analysis - Parts A and B)

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

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4 INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis of Study VX16-809-122 Parts A and B is based on the

- approved clinical study protocol, dated 04 December 2019, Version 2.0,
- approved Justification for Dose Selection Memorandum, dated 23 November 2020,
- approved eCRF, dated 10 March 2021, Version 15.1.

Study VX16-809-122 is a phase 3, 2-part, open-label study to evaluate the safety and pharmacokinetics of lumacaftor/ivacaftor combination therapy in subjects aged 1 to less than 2 years with cystic fibrosis, homozygous for the *F508del CFTR* mutation.

This SAP (Methods) documents the planned final analyses and data presentation for VX16-809-122.

[redacted] will perform the statistical analysis of the safety data; SAS® Version 9.4 Software (SAS Institute, Cary, North Carolina, USA) or higher will be used to generate all statistical outputs (tables, figures, listings and datasets).

The SAP methods Version 1.0 was finalized before the interim data snapshot for Part A Cohort 1. In this SAP Methods Version 2.0, modifications to the approved SAP Version 1.0 are made based on the amended protocol (Protocol Version 2.0) along with the Justification for Dose Selection Memorandum.

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) in subjects 1 to less than 2 years of age with cystic fibrosis (CF), homozygous for *F508del*

Part B

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

5.2 Secondary Objectives

Part A

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

Part B

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

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 and hematology), standard 12-lead ECGs, vital signs, pulse oximetry, and ophthalmologic examinations

6.2 Secondary Endpoint

Part A

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

Part B

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

[redacted]

[redacted]

7 STUDY DESIGN

7.1 Overall Design

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

7.1.1 Part A

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

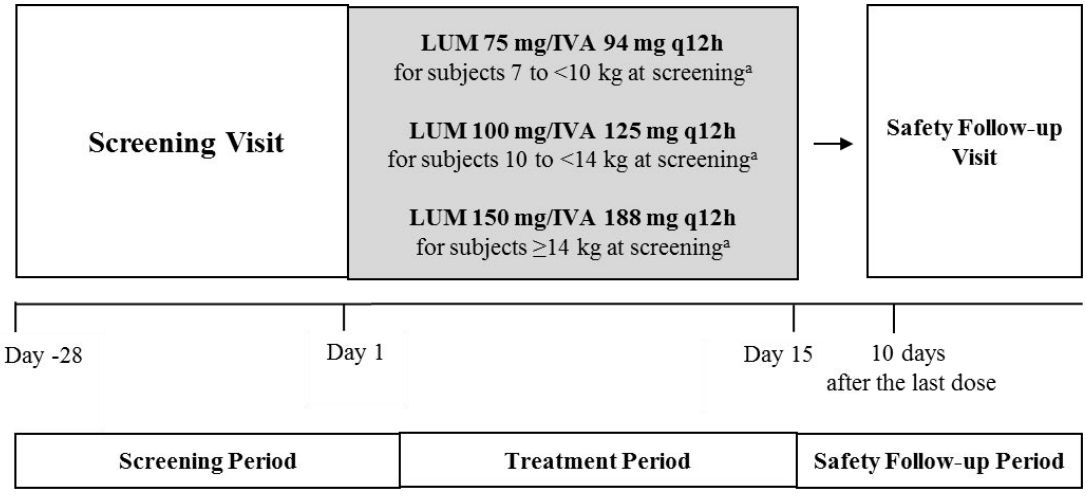
Approximately 10 subjects are planned for enrollment, including a minimum of 5 subjects 18 to <24 months of age (Cohort 1) and 5 subjects 12 to <18 months of age (Cohort 2). Subjects will be enrolled in Part A sequentially in the following cohorts:

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

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

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

Figure 7-1 Schematic of Study Design for Part A (Cohort 1 and Cohort 2)



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

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

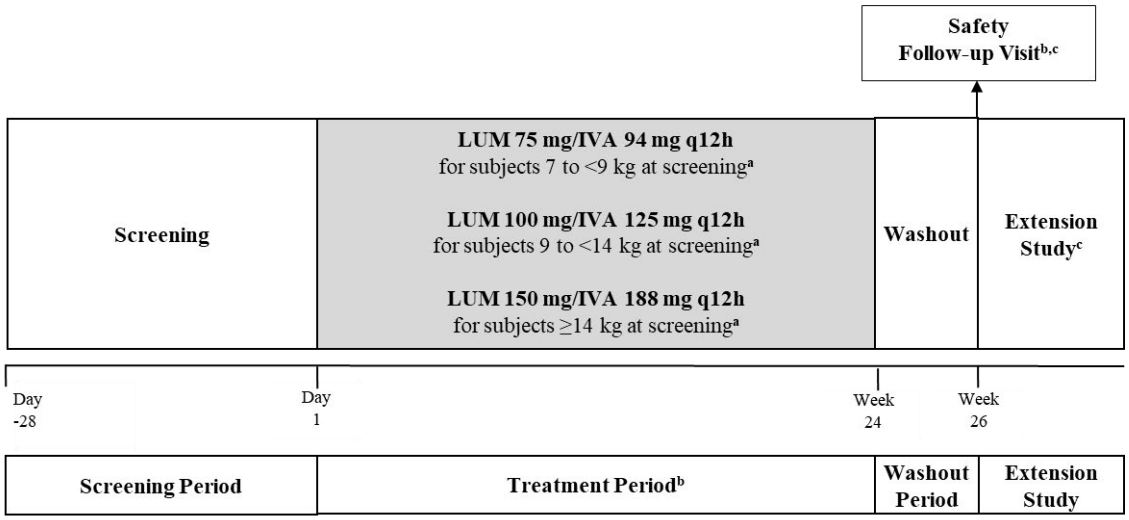
[a] Doses are based on the subject's weight at screening in Part A. No dose adjustments will be made across the duration of treatment. On Day 15, only the morning dose will be administered. Refer to Section 9.6.1 in Protocol Version 2.0 for additional study drug administration details.

7.1.2 Part B

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

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

Figure 7-2 Schematic of Study Design for Part B



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

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

[a] The doses and weight bounds listed above are those planned for Part B. Doses are based on the subject's weight at screening in Part B. No dose adjustments across the duration of treatment will be made. Refer to Section 9.6.2 in Protocol Version 2.0 for additional study drug administration details. The last dose of LUM/IVA in Part B will be the evening dose before the Week 24 Visit.

[b] Refer to Sections 9.1.3.2, 9.1.5.2, and 9.1.6.2 in Protocol Version 2.0 for details.

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

7.2 Sample Size and Power

Part A

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

Part B

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

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

Table 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%
27[a]	75.0%	94.2%

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

7.3 Randomization

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

7.4 Blinding and Unblinding

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

8 ANALYSIS SETS

8.1 All Subjects Set

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

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 for Part A will include all subjects who received at least 1 dose of study drug in Part A. The Part A safety analyses will be based on the Safety Set overall and by cohort, unless otherwise specified.

Safety Set for Part B will include all subjects who received at least 1 dose of study drug in Part B. The safety analyses will be based on the Safety Set overall, unless otherwise specified.

8.3 Full Analysis Set (for Part B only)

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.

[redacted]

9 STATISTICAL ANALYSIS

9.1 General Considerations

The Schedule of Assessments is provided in Appendix A.

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

Part A data will be summarized overall and by Cohort for the final clinical study report. The Part A primary safety conclusions will be based upon the overall group. Part B data will be summarized overall.

Separate interim analyses (IA) will be performed after:

- IA 1: all subjects in Cohort 1 have completed the last visit in Part A
- IA 2: all subjects in Cohort 2 have completed the last visit in Part A.

Interim analysis 1 for Cohort 1 will summarize safety data for Cohort 1 subjects only in a single column. Interim analysis 2 for Cohort 2 will summarize safety data for Cohort 2 subjects only in a single column. Details for the interim analyses are described in Section 10.1.

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). The precision standards are provided in an internal Biometrics document that specifies the programming rules including the precision for derived variables.

Categorical variables will be summarized using counts and percentages.

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

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 in each part.

[redacted]

[redacted]

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

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

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

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

- In the derivation of baseline measurements or last on-treatment visit.
- In individual subject data listings as appropriate.
- In the derivation of maximum/minimum values and maximum/minimum changes from baseline values.
- In scheduled visit windows per specified visit windowing rules (for Part B only).

Visit windowing rules:

For **Part A**, 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.

For **Part B:**

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 length [redacted] they will follow safety parameter visit window rules when evaluated as safety endpoints. [redacted]

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. All summaries will be based on the Safety Set and FAS.

9.2 Background Characteristics

Unless otherwise specified, this section applies to both Part A and Part B. All summaries will be provided based on the safety set of the corresponding Part, overall and by Cohort for Part A, and overall for Part B, unless otherwise specified. No statistical hypothesis testing will be performed.

9.2.1 Subject Disposition

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

- All Subjects Set
- Dosed (Safety Set)
- Enrolled but not dosed
- Enrolled and dosed (FAS, Part B only)

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

- Completed study drug treatment
- Prematurely discontinued the treatment and the reasons for discontinuations
- Completed study (i.e., completed Safety Follow-up Visit)
- Prematurely discontinued the study and the reasons for discontinuations
- Enrolled in a rollover extension study (for Part B only)

[redacted]

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

9.2.2 Demographics and Baseline Characteristics

Demographics, medical history and baseline characteristics will be summarized overall and by cohort for Part A, overall for Part B 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 for Part A and Part B will include the following:

- Weight (kg)
- Length (cm)
- BMI (kg/m^2)

Baseline characteristics for Part B only will include the following:

[redacted]

- Sweat Chloride

[redacted]

Sweat chloride at screening will be listed for Part A.

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 WHODrug, Global B3 format and categorized as the following:

- **Prior medication:** any medication that started before initial dosing of study drug, regardless of when it ended.
- **Concomitant medication:** medication continued or newly received on or after the first dose date of study drug of a study part through the end of the TE Period of the corresponding study part.
- **Post-treatment medication:** medication continued or newly received after the TE period in each study part.

A given medication can be classified as a prior medication, a concomitant medication, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment.

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

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

Prior medications and concomitant medications will be summarized descriptively using frequency tables by preferred name based on the Safety Set for each part.

Post-treatment medications will be listed for each subject.

9.2.4 Study Drug Exposure

Part A

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 and the ETT visit is available, use the ETT visit as the last dose date. Otherwise, if there is no ETT visit, the Safety Follow-up visit is used for analysis purposes.

Study drug exposure will be summarized descriptively in days overall and by Cohort based on Part A Safety Set.

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

Part B

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 and the ETT visit is available, use the ETT visit as the last dose date. Otherwise, if there is no ETT visit, the Safety Follow-up visit is used for analysis purposes.

Study drug exposure duration will be summarized overall based on the Part B Safety Set and descriptively as a quantitative variable.

Additionally, the cumulative duration of treatment exposure, defined as the sum of the subject's duration of treatment exposure and expressed in subject-years, will be provided. Duration of exposure will also be summarized as a categorical variable (>0 to ≤2 weeks, >2 to ≤4 weeks, >4 to ≤8 weeks, >8 to ≤16 weeks, >16 to ≤24 weeks, and >24 weeks).

9.2.5 Study Drug Compliance

Part A

A listing of exposure, with the first/last dose date/time, as well as the number of stick packs dispensed and returned will be provided to indicate the drug compliance.

Part B

Study drug compliance will be assessed by calculating as follows:

100 × (1 − [total number of days of study drug interruption] / [duration of study drug exposure + total number of days study drug interrupted after last dose, if any]).

The total number of days of study drug interruption is defined as the sum of (number of days of each study drug interruption), where number of days of each study drug interruption is defined as the interruption end date − the corresponding interruption start date + 1.

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.

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 overall 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.

Compliance will be presented in an individual subject data listing.

9.2.6 Important Protocol Deviations

An important protocol deviation (IPD) is a PD (any change, divergence, or departure from the study design or procedures defined in the protocol) that may significantly impact the completeness, accuracy and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. IPDs will be identified by the PD review team according to PD plan.
The programmable rules for identifying important protocol deviations based on the clinical database are defined in Appendix F.

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

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:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (serum chemistry and hematology)
- ECGs (standard 12-lead)
- Vital signs

- Pulse oximetry

Safety analyses will be performed overall and by cohort for Part A, overall for Part B based on 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 for each study part, defined as follows.

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

For AEs with 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 D.

TEAE summaries will be presented overall and by cohort for Part A, overall for Part B 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 strongest 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 strongest 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 (Part B only)

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

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

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

Note that 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.

Analysis of AEs of special interest (AESI) categories (Part B only):

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, serious AEs (SAEs) and deaths 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 treatment-emergent laboratory measurements, the raw values and change from baseline values of the continuous hematology and chemistry results will be summarized overall and by cohort for Part A, overall for Part B in SI units at each scheduled time point. Laboratory tests done in the local laboratory may be used in data analyses if data from the central laboratory are not available.

The number and percentage of subjects meeting a threshold analysis criterion during the TE Period will be summarized overall and by cohort for Part A, overall for Part B. The threshold analysis criteria are provided in Appendix E.

For hematology and chemistry, the number and percentage of subjects with abnormally low (<lower limit of normal [LLN]) value and with abnormally high (>ULN) values at each scheduled time point will be summarized overall and by cohort for Part A, overall for Part B.

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

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

9.4.3 Electrocardiogram

For treatment-emergent ECG measurements, a summary of raw values and change from baseline values will be provided at each scheduled time point for the following standard 12-lead ECG measurements: RR (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 meeting at least 1 threshold analysis criterion during the TE period will be summarized overall and by cohort for Part A, overall for Part B. The threshold analysis criteria are provided in Appendix E.

9.4.4 Vital Signs

For treatment-emergent vital signs measurements, the raw values and change from baseline values will be summarized overall and by cohort for Part A, overall for Part B 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), weight (kg), length (cm), and BMI (kg/m^2).

In addition, for both Part A and Part B, vital signs measurements at predose and the corresponding postdose timepoints (1 to 2 hours, and 4 to 6 hours) on Day 1 and Day 15 will be summarized, absolute change from predose to the corresponding postdose (1 to 2 hours, and 4 to 6 hours) on Day 1 and Day 15 will also be summarized.

The number and percentage of subjects with at least 1 potential abnormal SBP and DBP during the Treatment period will be summarized separately. The potential abnormal criteria are provided in Appendix G.
Potential abnormal SBP and DBP by their percentiles adjusted for sex, age and length 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 length adjustment will be based on length-for-age-z-scores and their corresponding percentiles using the standard normal distribution. The length percentiles will be further mapped per the following rules:

Table 9-1 Grouped Percentiles for Length-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 height percentiles is based on the SBP/DBP table provided 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). A listing of subjects with potentially abnormal SBP or DBP will be provided.

A listing of all vital signs parameters with their values at every visit (or time point) will be provided for each Part to be included in the CSR appendix.

9.4.5 Pulse Oximetry

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

In addition, for both Part A and Part B, oxygen saturation at predose and the corresponding postdose timepoints will be summarized (1 to 2 hours, and 4 to 6 hours) on Day 1 and Day 15, absolute change from predose to the corresponding postdose (1 to 2 hours, and 4 to 6 hours) on Day 1 and Day 15 will also be summarized.

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 TE Period will be provided.

9.4.6 Ophthalmological Examinations

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

9.4.7 Physical Examination

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

9.4.8 Other Safety Analysis

Not applicable.

9.5 Pharmacodynamic Analysis (Part B Only)

PD analyses [redacted] will be based on the FAS, and will be summarized overall. [redacted]

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., for samples with volumes <15 µL, the values will be considered missing for analysis purposes). If a subject has replicated measurements at a postbaseline time point, then the median of the values will be used in data analyses. The sweat chloride results for the left and right arms will be averaged and used in the analysis if the sweat chloride values for the left and right arms are both ≥15 µL; if only 1 arm is ≥15 µL, then only that value will be used. 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.

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

[redacted]

In addition, descriptive summary statistics, along with 95% confidence interval based on Normal approximation, will be provided for all other visits overall. Overall mean (95% CI) at each visit will be plotted.

[redacted]

[redacted]

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

Separate interim analyses (IA) will be performed after:

- IA 1: all subjects in Cohort 1 have completed the last visit in Part A
- IA 2: all subjects in Cohort 2 have completed the last visit in Part A.

The objective of the IAs is to confirm the dose selection for Part B and conduct the safety review.

The tables and listings will be generated as follows:

1. Disposition
2. Demographic

3. Baseline Characteristics
4. Exposure
5. Overall TEAE summary table
6. Incidence of TEAE by SOC and PT
7. Listing of Exposure
8. Listing of all SAEs
9. Listing of all AEs
10. Listing of Out of Normal Range (>ULN or <LLN) Chemistry
11. Listing of Out of Normal Range (>ULN or <LLN) Hematology
12. Listing of ECGs with Interpretation and findings
13. Listing of vital signs.

Safety data for each IA will be summarized in one column as an overall group only for Cohorts 1 and 2 respectively. Interim analysis 1 for Cohort 1 will report Cohort 1 subjects only. Interim analysis 2 for Cohort 2 subjects will report Cohort 2 subjects only.

10.2 IDMC Analysis

There will be no IDMC analysis for Part A. IDMC analyses are planned for Part B.

The IDMC's objectives and operational details were defined in a separate document (IDMC Charter) which was finalized before the first subject was dosed in the study. The IDMC's planned safety reviews of study data are outlined in the IDMC Charter. The details of the IDMC Statistical Analysis will be provided in the 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

Schedules of Assessments are shown in Table 12-1, Table 12-2 and Table 12-3.

Table 12-1 Study VX16-809-122: Part A and Part B Screening

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

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

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

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

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

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

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

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

[redacted]

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

[redacted]

Table 12-2 Study VX16-809-122: Part A Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Day 1	Day 3 (± 1 Day)	Day 8 (± 1 Day)	Day 15 (± 2 Days)	ETT Visit (As Soon As Possible After Last Dose of Study Drug)	Safety Follow-up Visit 10 (± 3) Days After the Last Dose of Study Drug
Clinic visit	X		X	X	X	X
Telephone contact[b]		X				
Safety Assessments						
Length and weight[c]	X			X	X	X
Vital signs[d]	X[e]		X	X[e]	X	X
Pulse oximetry[d]	X[e]		X	X[e]	X	X
Full physical examination[f]	X			X	X	X
Abbreviated physical examination	X[g]		X			
Standard 12-lead ECG[h]				X	X	X
Serum chemistry[i]	X[j]			X	X	X
Hematology[i]	X[j]			X	X	X
Observation 4 hours after the first dose	X					
Medications, treatments, and procedures review	Continuous from signing of ICF through Safety Follow-up Visit					
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit					
PK Assessments						
PK sampling	X[k]		X[l]	X[m]	X	
Study Drug Administration						
LUM/IVA dosing (dose based on weight at screening)[n]	**LUM/IVA q12h**					
Study drug count			X	X	X	

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 12-2 Study VX16-809-122: Part A Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Day 1	Day 3 (± 1 Day)	Day 8 (± 1 Day)	Day 15 (± 2 Days)	ETT Visit (As Soon As Possible After Last Dose of Study Drug)	Safety Follow-up Visit 10 (± 3) Days After the Last Dose of Study Drug

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

Table 12-3 Study VX16-809-122: Part B Treatment Period and Safety Follow-up Visit

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 12-3 Study VX16-809-122: Part B Treatment Period and Safety Follow-up Visit

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

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

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

[redacted]

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

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

[redacted]

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

Table 12-3 Study VX16-809-122: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Treatment Period									ETT Visit[b]	Safety Follow-up Visit (Week 26 [2 weeks ± 4 days After Last Dose])[c,d]
	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)		

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

Appendix B: Analysis Visit Window Mapping Rules for Safety and Pharmacodynamic Measurements (Part B only)

Table 12-4 Visit Window Mapping Rules for Safety and Pharmacodynamic Measurements

Assessments	Visit	Target Study Day	Visit Window (in study days)
Vital Signs Pulse oximetry LFT Chemistry	Day 15* Week 4 Week 8 Week 12 Week 16 Week 24 Safety Follow up	15 29 57 85 113 169	(1, 22] [23, 43] [44, 71] [72, 99] [100, 141] [142, 183] Use nominal visit
Sweat Chloride Non-LFT Chemistry Standard 12-lead ECG [redacted] Hematology	Week 4 Week 12 Week 24 Safety Follow up	29 85 169	(1, 57] [58, 127] [128, 183] Use nominal visit
[redacted]			
Microbiology Cultures	Week 12 Week 24	85 169	(1, 127] [128, 183]
Ophthalmologic exam	Week 24	169	(1, 183]

*Use predose nominal visit for vital signs/pulse oximetry at Day 15

Special handling for VS/Pulse Oximetry (for the change from predose to postdose analysis only):

For the change from predose to postdose VS/Pulse Oximetry analysis, no windowing rules are used.

1. The predose VS/ Pulse Oximetry on Day 1 and Day 15: analysis visit = nominal visit for Day 1 and Day 15, Predose correspondingly.
2. The post-dose VS/ Pulse Oximetry on Day 1 and Day 15: analysis visit = nominal postdose visits (1 to 2 hours, and 4 to 6 hours) on Day 1 and Day 15 correspondingly.

Appendix C: Assessments 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 12-5 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 Threshold Analysis

Table 12-5 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Clinical Chemistry		
ALT	≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >3xULN >5xULN >8xULN	FDA DILI Guidance Jul 2009.
AST	≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >3xULN >5xULN >8xULN	FDA DILI Guidance Jul 2009.
ALT or AST	ALT>3xULN or AST>3xULN ALT>5xULN or AST>5xULN ALT>8xULN or AST>8xULN	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	
Sodium	≤129 mmol/L ≥150 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.

Table 12-5 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	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).
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

Table 12-6 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
HR	≤70 bpm ≥150 bpm	
PR	≥150 ms	
QRS	≥80 ms	
QTcF	Absolute values (ms) Prolonged: >450 ms (Male and female)	To be applied to any kind of QT correction formula.

Appendix F: Important Protocol Deviation Programming Rules for Part B only (Based on the Clinical Database)

Important protocol deviations before first dose

- Inclusion criteria: Subjects (males and females) will be 1 to less than 1 years of age on Day 1 of the relevant par of study.

Important protocol deviation during the treatment period

- Compliance < 80%

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


Child_SBP_DBP.pdf