VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)
For Final Analysis

Protocol Number: VX19-809-124

A Phase 3, Open-label, and Rollover Study to Evaluate the Long-term Safety and Tolerability of Lumacaftor/Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Homozygous for *F508del* and 12 to <24 Months of Age at Treatment Initiation

[redacted]

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CF	cystic fibrosis
CFTR	CF transmembrane conductance regulator protein
CI	confidence interval
CMQ	Custom MedDRA Queries
CRF	case report form
DBP	diastolic blood pressure
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
HR	heart rate
ICF	informed consent form
IPD	important protocol deviation
IRT	immunoreactive trypsin and trypsinogen
IVA	Ivacaftor
LFT	liver function test
LLN	lower limit of normal
LUM	Lumacaftor
MedDRA	Medical Dictionary for Regulatory Activities
NHLBI	National Heart, Lung, and Blood Institute
OE	ophthalmological examination
PD	pharmacodynamics(s)
PE	physical examination
PR	PR interval
PT	preferred term
PY	patient-year: a patient with 48 weeks of treatment-emergent duration
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
RR	interval from the onset of 1 QRS complex to the next
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure

SD	standard deviation
SE	standard error
SFU	safety follow-up
SI	SI units (International System of Units)
SOC	system organ class
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary

3 MODIFICATIONS

3.1 Modifications to the Approved Clinical Study Protocol

Typographical and administrative changes were made to improve the clarity of the document.

3.2 Modifications to the Approved Statistical Analysis Plan

This is the first version of the SAP (Methods) for the final analysis.

3.3 Modifications to the Approved IDMC Charter

None.

4 INTRODUCTION

Study VX19-809-124 is a Phase 3, open-label, and rollover study to evaluate the long-term safety and tolerability of Lumacaftor/Ivacaftor (LUM/IVA) treatment in subjects with cystic fibrosis (CF) who are homozygous for *F508del* and 12 to <24 months of age at treatment initiation.

This statistical analysis plan (SAP) is for the final analysis of Study VX19-809-124 (Study 124) data and is based on the:

- approved clinical study protocol, dated 12 February 2021, Version 2.0
- approved electronic case report form (eCRF), dated 10 April 2021, Version 6.0

This SAP (Methods) documents the planned statistical methods and data presentations of the final analysis for Study 124. It also documents additional analyses not prespecified in the protocol, but necessary for the scientific understanding of the drug entity.

The Vertex Biometrics Department or designee will perform the statistical analysis described in this document; SAS (Version 9.4 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets).

This SAP will be finalized and approved prior to the data cut for the final analysis of Study 124. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP.

5 STUDY OBJECTIVES

5.1 Primary Objective

To evaluate the safety and tolerability of long-term LUM/IVA treatment in subjects with CF, who are homozygous for *F508del* and 12 to <24 months of age at treatment initiation.

5.2 Secondary Objective

To evaluate the pharmacodynamics (PD) of long-term LUM/IVA treatment in subjects with CF, who are homozygous for *F508del* and 12 to <24 months of age at treatment initiation.

5.3 Other Objectives

Not Applicable.

6 STUDY ENDPOINTS

6.1 Primary Endpoint

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

6.2 Secondary Endpoint

Absolute change from baseline in sweat chloride.

6.3 Exploratory Endpoints

Absolute change from baseline in the following growth parameters:

- Body mass index (BMI)-for-age z-score and BMI
- Weight-for-age z-score and weight

- Length/height-for-age z-score and length/height
- Weight-for-length z-score

Absolute change from baseline in the following markers of pancreatic function:

- Fecal elastase-1 (FE-1) levels
- Serum immunoreactive trypsin and trypsinogen (IRT) levels

Absolute change from baseline in fecal calprotectin, a marker of intestinal inflammation.

7 STUDY DESIGN

7.1 Overall Design

This is a Phase 3, multicenter, open-label study in subjects who are 12 to <24 months of age at initiation of LUM/IVA treatment (

Figure 7-1). The study will enroll approximately 50 subjects.

Rollover Subjects

Subjects who participated in parent study VX16-809-122 Part B (Study 122B) and meet all eligibility requirements can rollover into Study 124.

For rollover subjects at sites activated by the Study 122B Safety Follow-up (SFU) Visit, their Study 124 Day 1 Visit will be on the same day as their Study 122B SFU Visit; any Study 124 Day 1 assessments that are specified to be performed at the Study 122B SFU Visit will not need to be repeated.

If the Study 124 Day 1 Visit does not coincide with the Study 122B SFU Visit, and if Study 124 Day 1 is ≤9 days after the Study 122B SFU Visit, the Study 124 Day 1 assessments will not need to be repeated. Otherwise, if Study 124 Day 1 is >9 days after the Study 122B SFU Visit, the subject will need to complete all Study 124 Day 1 assessments (except the OE if it was performed ≤12 weeks before the Study 124 Day 1 Visit).

Rollover subjects may receive treatment for up to 120 weeks (24 weeks in Study 122B and 96 weeks in Study 124).

LUM/IVA-naïve Subjects

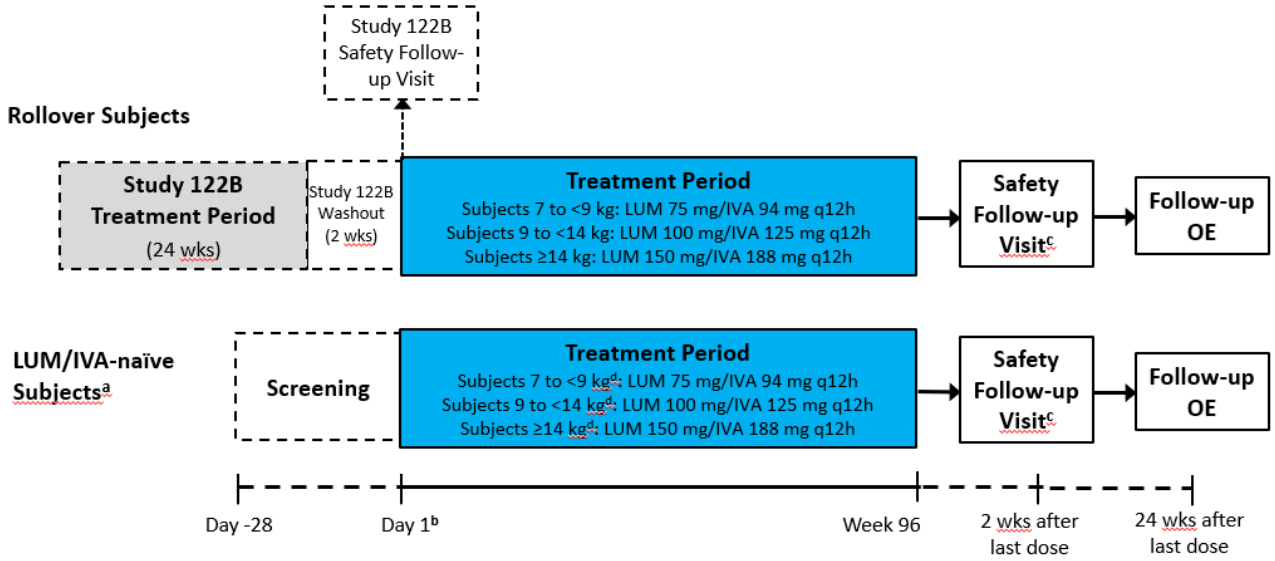
Subjects who did not participate in Study 122B and are 12 to <24 months of age at Study 124 Day 1 can enroll by age group if they meet Study 124 eligibility requirements:

- Subjects who are 18 to <24 months of age can enroll in Study 124 after a minimum of 10 subjects (aged 18 to <24 months) have enrolled in Study 122B and after an assessment of safety data from Study 122B through Week 12 for ≥5 subjects aged 18 to <24 months.
- Subjects who are 12 to <18 months of age can enroll in Study 124 after a minimum of 10 subjects (aged 12 to <18 months) have enrolled in Study 122B and after an assessment of safety data from Study 122B through Week 12 for ≥5 subjects aged 12 to <18 months.

Note: Subjects aged 18 to <24 months will start enrolling in Study 124 before any subjects 12 to <18 months of age can enroll as a result of the staggered timing from the Study 122 study design, which includes sequential age cohorts.

LUM/IVA-naïve subjects may receive treatment for up to 96 weeks in Study 124.

Figure 7-1 Schematic of Study 124 Design



IVA: ivacaftor; LUM: lumacaftor; OE: ophthalmological examination; q12h: every 12 hours; wks: weeks

[a] LUM/IVA-naïve subjects (by age group: 18 to <24 months and 12 to <18 months) will be able to enroll in Study 124 once minimum enrollment has been met in Study 122B (n = 10 subjects in each age group), and after an assessment of safety data from Study 122B through Week 12 for ≥5 subjects in each age group.

[b] For rollover subjects, the Day 1 Visit should be the same day as the Safety Follow-up Visit in Study 122B.

[c] The Safety Follow-up Visit will not be required for subjects transitioning to commercial LUM/IVA.

[d] For LUM/IVA-naïve subjects, doses will be determined by weight at screening.

7.2 Sample Size and Power

No formal sample size calculations have been performed for this study. The study will enroll approximately 50 subjects to provide data for the assessment of long-term safety in the target patient population, as requested by a regulatory agency.

7.3 Randomization

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

7.4 Blinding and Unblinding

This is an open-label study.

8 ANALYSIS SETS

The following analysis sets are defined. Enrolled subjects are those who signed consent/assent form and had an enrollment date in the database.

All Subjects Set: All subjects who are enrolled or dosed in Study 124. This analysis set will be used for individual subject data listings and disposition summary tables unless otherwise specified.

Safety Set: All subjects who are exposed to any amount of study drug in Study 124. This analysis set will be used for all safety analysis unless otherwise specified.

Full Analysis Set: All subjects who are enrolled and dosed in Study 124. This analysis set will be used for all analysis of PD and exploratory endpoints unless otherwise specified.

9 ANALYSIS PERIOD

The analysis periods are described below.

The **Treatment-emergent (TE) Period** will start on or after the first dose date of study drug in Study 124 to 18 days (inclusive) after the last dose date of study drug in Study 124 or up to the last day in Study 124, whichever occurs first.

10 STATISTICAL ANALYSIS

10.1 General Considerations

The Schedule of Assessments is provided in the CSP for Study 124. The precision standards for reporting safety and efficacy variables are provided in an internal Biometrics document that specifies the programming rules including the precision for derived variables.

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

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

Categorical variables will be summarized using counts and percentages.

Baseline value will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected on or before the first dose of LUM/IVA in Study 124.

For sweat chloride, values at each visit will be based on averaged measurements from left and right arms. For Rollover Subjects, baseline will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected on or before the first dose of LUM/IVA in Study 124. For LUM/IVA-naïve Subjects, baseline will be defined as the average of the values at screening and the pretreatment measurement on Day 1 of Study 124. 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.

Unscheduled visits will be included in the analysis as follows:

- In scheduled visit windows per specified visit windowing rules
- In the derivation of baseline measurements or last on-treatment visit
- In individual subject data listings, as appropriate
- In the derivation of max/min values and max/min change from baseline values

Visit windowing rules: Appendix defines the visit window mapping rules to derive the analysis visits for Study 124.

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.
- If there are local lab results and central lab results at same visit point, then the central lab results will be used.

BMI, weight, and length will follow PD parameter visit window rules when evaluated as PD endpoints; they will follow safety parameter visit window rules when evaluated as safety endpoints. Their corresponding z-scores will be assigned analysis visit window rules the same as BMI, weight, and length, respectively.

For clinical laboratory, ECG and vital sign measurements collected on the date of the first dose of study drug, if it cannot be determined whether the measurement was taken before or after the first dose, scheduled measurements will be treated as pre-dose observations, and unscheduled measurements will be treated as post-dose observations.

If ETT visit happens on or after 10 days of last LUM/IVA dose and there are no SFU assessments collected, then ETT Visit will be mapped to SFU Visit.

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

10.2.1 Subject Disposition

The number of subjects in the following categories for the population will be provided:

- All Subjects Set
- Safety Set
- FAS
- Enrolled but never dosed

Number and percentage (based on the Safety Set) of subjects in each of the following categories will be provided:

- Completed study drug treatment
- Prematurely discontinued study drug treatment and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation

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

Demographics and baseline characteristics will be summarized based on Safety Set.

Demographic data will include the following:

- Sex (male and female)
- Age at treatment initiation (months)
- Age group at treatment initiation
- Ethnicity (Hispanic or Latino; Not Hispanic or Latino; 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; Other)

Baseline characteristics will include the following:

- Weight (kg)
- Length/height (cm)

- BMI (kg/m^2)
- Weight-for-age z-score
- Length/height-for-age z-score
- BMI-for-age z-score
- Weight-for-length/height z-score
- Sweat chloride (mmol/L)
- FE-1 Levels (mg/kg)
- Serum IRT Levels (ug/L)
- Fecal Calprotectin Levels (mg/kg)

Medical history will be summarized based on Safety Set using the Medical Dictionary for Regulatory Activities (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 will be coded using the World Health Organization Drug Dictionary (WHODrug) and categorized as the following:

Prior medication: Any medication that started before the date of the first dose of study drug in Study 124.

Concomitant medication: Any medication continued or newly received during the TE Period.

Post-treatment medication: Any medication continued or newly received after the end of the TE Period.

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

Prior medications and concomitant medications will be summarized descriptively using frequency tables by preferred name and by ATC level 1 and 2 based on Safety Set.

All medications will be listed for each subject.

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

10.2.4 Study Drug Exposure

Duration of study drug exposure is defined as follows: last dose date in the TE Period − first dose date in the TE Period + 1 day, regardless of any dose interruptions. 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 last known study participation date will be used for analysis purposes.

Duration of study drug exposure as well as number of sticks administered, defined as (total number of sticks dispensed) − (total number of sticks returned), will be summarized descriptively based on the Safety Set for the the TE Period. Additionally, the total duration of treatment exposure, defined as the sum of the subject's duration of treatment exposure and expressed in patient-years (1 patient-year is defined as one patient with 48 weeks of treatment), will be provided.

Study drug administration data will be presented in individual subject data listings.

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 calculated as follows: 100 × (1 − [total number of days of study drug interruption in the TE Period] / [duration of study drug exposure]).

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

Percent of stick packs taken will be calculated as follows: 100 × (total number of stick packs administered) / (2 × [duration of study drug exposure in the TE Period]).

Treatment compliance percentages and percent of stick packs taken will be summarized descriptively based on the 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.

Study drug compliance and study drug interruption data will be presented in individual subject data listings in addition.

10.2.6 Important Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedure defined in the protocol. An important protocol deviation (IPD) is a protocol deviation 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 Protocol Deviation Review Team according to the Protocol Deviation Plan.

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

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

10.3 Efficacy Analysis

Not applicable.

10.4 Secondary Endpoint Analysis

10.4.1 Absolute Change from Baseline in Sweat Chloride

For each subject and at each time point, two sweat chloride measurements will be collected: one from the right arm and one from the left arm. Of the two measurements, only sweat chloride values obtained from sample volume ≥15 µL will be included in any analysis as a sample volume of at least 15 µL is required for testing. If a subject has replicated measurements at a postbaseline time point, then the median of the values will be used in data analyses. If the sweat chloride values for the left and right arms are both from sample volume ≥15 µL, these values will be averaged together for the analysis; if only one arm is from sample volume ≥15 µL, 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 baseline in sweat chloride at each visit will be summarized descriptively (n, mean, SD, SE, median, minimum, and maximum) based on the FAS. In addition, the 95% confidence interval (CI) based on Normal approximation of the absolute change from baseline values will be provided. The mean (95% CI) of the absolute change from baseline at each scheduled time point will be plotted.

10.5 Exploratory Endpoint Analysis

10.5.1 Absolute Change from Baseline in Growth Parameters

Absolute Change from Baseline in BMI-for-Age Z-score and BMI

BMI z-score will be calculated by using WHO BMI-for-age charts. The BMI-for-age z-score will be calculated as follows:

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

Where X is the derived BMI value in kg/m^2 based on the raw weight and raw height and L, M, and S are selected from the WHO BMI-for-age charts by subject sex and age. The BMI-for-AGE z-score tables contain these parameters by sex and age; they are available at (accessed Jun 09, 2023):

- https://www.who.int/toolkits/child-growth-standards/standards/body-mass-index-for-age-bmi-for-age

Raw values and absolute change from baseline in BMI and BMI-for-age z-score at each visit will be summarized descriptively (n, mean, SD, SE, median, minimum, and maximum) based on the FAS. In addition, the 95% CI of the absolute change from baseline values will be provided. The mean (95% CI) of the absolute change from baseline values will be plotted at each scheduled visit.

Absolute Change from Baseline in Weight-for-Age Z-score and Weight

Weight-for-age z-score will be calculated by using WHO weight-for-age tables. The same equation used to calculate BMI-for-age z-score will be used to calculate weight-for-age z-score, where *X* in the equation will be the collected weight. *L*, *M*, and *S* parameters will be selected from the WHO weight-for-age tables. The weight-for-age z-score tables contain these parameters by sex and age; they are available at (accessed Jun 09, 2023):

- https://www.who.int/tools/child-growth-standards/standards/weight-for-age

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

Absolute Change from Baseline in Length/Height-for-Age Z-score and Length/Height

Length-for-age z-score will be calculated by using WHO length-for-age tables. The same equation used to calculate BMI-for-age z-score will be used to calculate length-for-age z-score, however *X* in the equation will be the collected length. *L*, *M*, and *S* parameters will be selected from the WHO length -for-age tables. The length-for-age z-score tables contain these parameters by sex and age; they are available at (accessed Jun 09, 2023):

- https://www.who.int/tools/child-growth-standards/standards/length-height-for-age

See Appendix G Computing Z-Scores Using WHO Standards for further details on determining length/height and necessary adjustment.

Length/height-for-age z-score and length/height will be analyzed in a similar way to BMI-for-age z-score and BMI.

Absolute Change from Baseline in Weight-for-Length Z-Score

Weight-for-length z-score will be calculated by using WHO weight-for-length tables. The same equation used to calculate BMI-for-age z-score will be used to calculate weight-for-length z-score, where *X* in the equation will be the collected weight. *L*, *M*, and *S* parameters will be selected from the WHO weight-for-length/height tables. The weight-for-length z-score tables contain these parameters by sex and length/height; they are available at (accessed Jun 09, 2023):

- https://www.who.int/tools/child-growth-standards/standards/weight-for-length-height

See Appendix G Computing Z-Scores Using WHO StandardsG for further details on determining length/height and necessary adjustment.

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

10.5.2 Absolute Change from Baseline in Markers of Pancreatic Function

Absolute Change from Baseline in FE-1 Levels

Raw values and absolute change from baseline in FE-1 levels at each visit will be summarized descriptively (n, mean, SD, SE, median, minimum, and maximum) based on the FAS. In addition, the 95% CI of the absolute change from baseline values will be provided.

In addition, the number and percentage of subjects with FE-1 levels consistent with pancreatic insufficiency (defined as FE-1 level <200 mg/kg) will be provided at baseline and at each visit.

The number and percentage of subjects with shift changes from baseline at each visit will be summarized using the following two categories: <200 mg/kg; ≥200 mg/kg.

The mean (95% CI) of the absolute change from baseline in FE-1 values will be plotted at each scheduled visit.

Absolute Change from Baseline in Serum IRT Levels

Raw values and absolute change from baseline in serum IRT levels at each visit will be summarized descriptively (n, mean, SD, SE, median, minimum, and maximum) based on the FAS. In addition, the 95% CI of the absolute change from baseline values will be provided.

The mean (95% CI) of the absolute change from baseline in serum IRT values will be plotted at each scheduled visit.

10.5.3 Absolute Change from Baseline in Fecal Calprotectin

Raw values and absolute change from baseline in fecal calprotectin levels at each visit will be summarized descriptively (n, mean, SD, SE, median, minimum, and maximum) based on the FAS. In addition, the 95% CI of the absolute change from baseline values will be provided. The mean (95% CI) of the absolute change from baseline in fecal calprotectin values will be plotted at each scheduled visit.

10.6 Safety Analysis

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

- AEs
- Clinical laboratory measurements (serum chemistry and hematology)
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry
- Physical Examinations
- OEs

Safety endpoints will be summarized descriptively based on the Safety Set.

All listings will be provided based on the All Subjects Set.

10.6.1 Adverse Events

AEs will be classified as pretreatment AEs, treatment-emergent adverse events (TEAEs), or post-treatment AEs, defined as follows:

Pretreatment AE: Any AE that started before the first dose date of study drug in Study 124.

TEAE: Any AE that worsened (either in severity or seriousness) or that was newly developed on or after the first dose date of study drug through the end of the TE Period.

Post-treatment AE: Any AE that increased in severity or was newly developed after the TE Period.

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

Details for imputing missing or partial start dates of AEs are described in Appendix .

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

An overview of the TEAE profile will be provided, including total number of TEAEs, with number and percentage of subjects and for the following categories: (1) Any TEAEs; (2) Grade 3/4 TEAEs; (3) TEAEs by Strongest Relationship to the Drug; (4) TEAEs by Maximum Severity; (5) TEAEs Leading to Treatment Interruption; (6) TEAEs Leading to Treatment Discontinuation; (7) Serious TEAEs; (8) Related Serious TEAEs; (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
- TEAEs by Maximum Severity
- Related TEAEs
- TEAEs Leading to Treatment Interruption
- TEAEs Leading to Treatment Discontinuation
- Serious TEAEs
- Related Serious TEAEs
- TEAEs Leading to Death
- Frequently Reported TEAEs (≥5% at the PT level)

These summaries will be presented by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with any event) and exposure-adjusted number of events in 100PY. When summarizing the number of events, a subject with multiple events within a category is counted multiple times in that category. When

summarizing the number and percentage of subjects with any 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 only the strongest relationship level will be presented in the relationship summaries.

Additional summary table in which the frequency counts and percentages will be presented for TEAEs during the TE period for the following:

• All TEAEs by PT

• Non-Serious TEAEs by SOC and PT

• Related Non-Serious TEAEs by SOC and PT

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

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):

Three types of AESIs are proposed for Study 124; the Customized MedDRA Queries (CMQ) used may change before database lock.

1. Elevated Transaminases AESI

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

   - 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 AESI of respiratory symptoms is defined as AEs whose PTs fall into any of the following categories:

- Chest discomfort
- Dyspnoea
- Respiration abnormal

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

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

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

TE AESIs will be summarized using the Safety Set by:

1. Number and percentage of subjects by PT
2. Number and percentage of subjects by Maximum Severity
3. Descriptive summary of duration of events (days)
4. Descriptive summary of time-to-onset of the first event (days, relative to first dose date)
5. Number and percentage of subjects with exposure-adjusted number of events in 100PY for: (1) TEAEs Leading to Treatment Interruption; (2) TEAEs Leading to Treatment Discontinuation; (3) Serious TEAEs; (4) Related Serious TEAEs; and (5) TEAEs Leading to Death

10.6.2 Clinical Laboratory

For laboratory measurements, raw values and change from baseline values for the continuous hematology and chemistry results will be summarized in SI units at each visit of the TE Period.

Laboratory tests done in the local laboratory may be used in data analyses if data from the central laboratory are not available.

For hematology and chemistry, the number and percentage of subjects with abnormally low (< lower limit of normal [LLN]) values and with abnormally high (> upper limit of normal [ULN]) values at each visit will be summarized.

The number and percentage of subjects meeting the threshold analysis criterion during the TE Period of the TE Period will be summarized for selected laboratory parameters based on the Safety Set. The threshold analysis criteria are provided in Appendix .

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

LFT elevations meeting ALT or AST > 5xULN, or ALT > 3xULN and total bilirubin > 2xULN, or AST > 3xULN and total bilirubin > 2xULN at one visit during the TE period will also be listed.

10.6.3 Electrocardiogram

For ECG measurements, raw values and change from baseline values will be summarized at each visit of the TE Period for the following standard digital ECG measurements: RR (ms), PR (ms), QT (ms), QT corrected for HR (QTc) intervals (Fridericia's correction QTc (ms) = $QT/RR^{1/3}$), QRS duration (ms), and HR (bpm). In addition, the mean value (95% CI) at each visit will be plotted for QTc.

The number and percentage of subjects meeting the threshold analysis criterion during the TE Period of the TE Period will be summarized for selected ECG parameters based on the Safety Set. The threshold analysis criteria are provided in Appendix .

Listings will be provided for the ECG measurements.

10.6.4 Vital Signs

For vital signs measurements, raw values and change from baseline values will be summarized at each visit of the TE Period for the following parameters: systolic and diastolic blood pressure (SBP/DBP) (mmHg), temperature (°C), pulse rate (beats per minute), respiratory rate (breaths per minute), weight (kg), length/height (cm), and BMI (kg/m^2).

The number and percentage of subjects with at least one potentially abnormal SBP and/or DBP during the TE Period of the TE Period will be summarized separately based on the Safety Set using threshold criteria provided in Appendix . Potentially abnormal SBP and DBP by percentile (adjusted for sex, age, and length/height) will be provided, including:

- Number and percentage of subjects in categories: ≥90% to <95%; ≥95% to <99% + 5 mmHg; ≥99% + 5 mmHg, during the TE Period
- Number and percentage of subjects with SBP and DBP percentiles ≥95% at least once and at least twice during the TE Period
- Number and percentage of subjects with SBP and DBP percentiles ≥95% at each visit in the TE Period

The length/height adjustment will be based on length/height-for-age z-scores and their corresponding percentiles using the standard normal distribution (Appendix). The length/height percentiles will be further mapped per the following rules displayed in Table 9-1:

Table 9-1 Grouped Percentiles for Length/Height-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 length/height percentile is based on the SBP/DBP table on 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, accessed Oct 26, 2021).

Listings of subjects with potentially abnormal SBP and/or DBP will be provided.

The mean (+/- SD) value at each visit will be plotted separately for SBP and DBP.

Listings will be provided for vital signs parameters.

10.6.5 Physical Examination

Listings will be provided for physical examination findings.

10.6.6 Pulse Oximetry

For pulse oximetry measurements, raw values and change from baseline values will be summarized at each visit of the TE Period for the percent of oxygen saturation by pulse oximetry.

The number and percentage of subjects with shift changes from baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the TE Period of the TE Period will be summarized based on the Safety Set.

Listings for pulse oximetry measurements will be included in vital signs listings.

10.6.7 Ophthalmological Examinations

OE findings will be presented as data listings.

10.6.8 COVID-19 Impacted Visits

A listing containing subjects' visits impacted due to COVID-19 will be provided.

11 LIST OF APPENDICES

Appendix A Analysis Visit Windows for Safety and Pharmacodynamic Assessments

Table 11-1 Visit Window Mapping Rules for Rollover Subjects (809-124)

Assessments	Visit	Target Study Day	Visit Window (in study days)
• Weight and length/height • Vital signs • Pulse oximetry • Labs o LFTs Only	Day 15	15	(1, 50]
	Week 12	85	[51, 127]
	Week 24	169	[128, 211]
	Week 36	253	[212, 295]
	Week 48	337	[296, 379]
	Week 60	421	[380, 463]
	Week 72	505	[464, 547]
	Week 84	589	[548, 631]
	Week 96	673	[632, 680]
	Follow-up Visit	687	Nominal Visit
• IRT • Labs o Chemistry o Hematology	Week 12	85	(1, 127]
	Week 24	169	[128, 211]
	Week 36	253	[212, 295]
	Week 48	337	[296, 379]
	Week 60	421	[380, 463]
	Week 72	505	[464, 547]
	Week 84	589	[548, 631]
	Week 96	673	[632, 680]
	Follow-up Visit	687	Nominal Visit
• Standard 12-Lead ECG • Sweat chloride • Fecal Sample o Fecal Calprotectin o Fecal Elastase-1	Week 24	169	(1, 253]
	Week 48	337	[254, 505]
	Week 96	673	[506, 680]
	Follow-up Visit	687	Nominal Visit
• Ophthalmological Examination	Week 24	169	(1, 253]
	Week 48	337	[254, 421]
	Week 72	505	[422, 589]
	Week 96	673	[590, 680]
	Follow-up Visit	687	Nominal Visit

If ETT visit happens on or after 10 days of last LUM/IVA dose and there are no SFU assessments collected, then ETT Visit will be mapped to SFU analysis Visit.

Table 11-2 Visits Window Mapping Rules for LUM/IVA-naïve Subjects (809-124)

Assessments	Visit	Target Study Day	Visit Window (in study days)
• Weight and length/height • Vital signs • Pulse oximetry • Labs ○ LFTs Only	Day 15	15	(1, 22]
	Week 4	29	[23, 43]
	Week 8	57	[44, 71]
	Week 12	85	[72, 99]
	Week 16	113	[100, 141]
	Week 24	169	[142, 211]
	Week 36	253	[212, 295]
	Week 48	337	[296, 379]
	Week 60	421	[380, 463]
	Week 72	505	[464, 547]
	Week 84	589	[548, 631]
	Week 96	673	[632, 680]
	Follow-up Visit	687	Nominal Visit
• Standard 12-Lead ECG	Week 4	29	(1, 57]
	Week 12	85	[58, 127]
	Week 24	169	[128, 253]
	Week 48	337	[254, 505]
	Week 96	673	[506, 680]
	Follow-up Visit	687	Nominal Visit

• Labs
  ○ Chemistry
  ○ Hematology
	Week 4	29	[23, 43]

	Week 8	57	[44, 71]
	Week 12	85	[72, 99]
	Week 16	113	[100, 141]
	Week 24	169	[142, 211]
	Week 36	253	[212, 295]
	Week 48	337	[296, 379]
	Week 60	421	[380, 463]
	Week 72	505	[464, 547]
	Week 84	589	[548, 631]
	Week 96	673	[632, 680]
	Follow-up Visit	687	Nominal Visit
• IRT	Week 4	29	(1, 57]
	Week 12	85	[58, 127]
	Week 24	169	[128, 211]
	Week 36	253	[212, 295]
	Week 48	337	[296, 379]
	Week 60	421	[380, 463]
	Week 72	505	[464, 547]
	Week 84	589	[548, 631]
	Week 96	673	[632, 680]
	Follow-up Visit	687	Nominal Visit

• Sweat chloride • Fecal Sample	Week 4	29	(1, 57]
	Week 12	85	[58, 127]
	Week 24	169	[128, 253]
	Week 48	337	[254, 505]
	Week 96	673	[506, 680]
	Follow-up Visit	687	Nominal Visit
• Ophthalmological Examination	Week 24	169	(1, 253]
	Week 48	337	[254, 421]
	Week 72	505	[422, 589]
	Week 96	673	[590, 680]
	Follow-up Visit	687	Nominal Visit

The study days are based on the first dose in Study 124.
For Vital signs the Nominal Day 15 predose assessments will be mapped to Day 15.

Appendix B Imputation Rules for Missing Prior/Concomitant Medication Dates

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

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use the informed consent 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 practice, use the end of study date to impute).

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

Table 11-3 Prior, Concomitant, and Post Categorization of a Medication

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

A: Post; C: Concomitant; P: Prior; TE: treatment-emergent

Appendix C Imputation Rules for Missing AE dates

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

If only Day of AE start date is missing:

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

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

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

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

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

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

If Year of AE start date is missing:

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

Appendix D Criteria for Threshold Analysis

Table 11-4 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	
Sodium	≤129 mmol/L ≥150 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.

Parameter	Categorical change	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 10-5 Threshold Analysis Criteria for ECGs

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

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

https://www.nhlbi.nih.gov/sites/default/files/media/docs/hbp_ped.pdf (pages: 10-13; accessed Oct 26, 2021)

Appendix F Programmable Important Protocol Deviation Programming Rules (Based on the Clinical Database)

Important Protocol Deviations during the Treatment Period:

- Compliance < 80% in Study 124
- Rollover Subject Study 122B completion
- LUM/IVA-naïve Subject age and inclusion/exclusion criteria

Appendix G Computing Z-Scores Using WHO Standards

Adjusting Length/Height for Recumbent vs. Standing Position

In calculation of z-scores relating to length/height, an adjustment may be necessary depending on how the length/height data were collected and the child's age (World Health Organization, 2006; Schumacher, 2020).

*If the Measures are **KNOWN** to Be Either Recumbent Length or Standing Height:*

- If the subject's age is ≤ 24 Months (730 days), measure of recumbent length should be used. If standing height measure is collected instead, **0.7 cm must be ADDED** to the standing height measure to adjust.
- If the subject's age is > 24 Months (730 days), measure of standing height should be used. If recumbent length measure is collected instead, **0.7 cm must be SUBTRACTED** from the recumbent length measure to adjust.

*If the Measures are **UNSPECIFIED** to Be Either Recumbent Length or Standing Height:*

- *If **AGE at the Visit is Not Missing***
  - If child age is ≤ 24 Months (730 days), the measure is to be considered as recumbent length
  - If child age is > 24 Months (730 days), the measure is to be considered as standing height
- *If **Age at the Visit is Missing***
  - If the measure is < 87cm, it is to be considered as recumbent length
  - If the measure is ≥ 87cm, it is to be considered as standing height

If necessary, all ages collected in months can be converted to days using 1 month = 30.4375 days.

Linear Interpolation of Length/Height Measurements

The WHO standard tables for Weight-for-Length/ Height comes with tabulated Length/Height (X) values with 1 decimal place and at 0.1 intervals. In practice, if the collected Length/Height (X) values fall between the intervals, the following interpolation approach is suggested to obtain the appropriate values for L, M, and S (World Health Organization, 2006):

1. Round the **Length/Height** (X) to the nearest 1 decimal place value lower than the collected value (e.g., round 73.265 to 73.2), and obtain the L, M, and S values using the standard table. Let us denote the rounded value as (X_l) and the tabulated values as L_l, M_l, and S_l.
2. Round the **Length/Height** to the nearest 1 decimal place value higher than the collected value (e.g., round 73.265 to 73.3), and obtain the L, M, and S values using

the standard table. Let us denote the rounded value as (X_u) and the tabulated values as L_u, M_u, and S_u.

3. Obtain the interpolated values of L, M, and S as:

$$L^* = L_l + \left(\frac{X - X_l}{0.1}\right)(L_u - L_l)$$

$$M^* = M_l + \left(\frac{X - X_l}{0.1}\right)(M_u - M_l)$$

$$S^* = S_l + \left(\frac{X - X_l}{0.1}\right)(S_u - S_l)$$

Finally, use the values L^*, M^*, and S^* in z-score calculations.

Adjustment for Weight-based z-scores in the Extreme Tails of the Distribution

The weight-based z-scores (e.g., Weight-for-Age, Weight-for-Length, Weight-for-Height, and BMI-for-Age) beyond ±3 SD need to be adjusted (World Health Organization, 2006) as described in following:

1. Calculate the initial z-score using the following formula, as described above:

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

2. Compute the final z-score (z^*) of the child as:

$$z^* = \begin{cases} z & , \quad \text{if } |z| \leq 3 \\ 3 + \left(\dfrac{X - \mathrm{SD}_{3\mathrm{POS}}}{\mathrm{SD}_{23\mathrm{POS}}}\right) & , \quad \text{if } z > 3 \\ -3 + \left(\dfrac{X - \mathrm{SD}_{3\mathrm{NEG}}}{\mathrm{SD}_{23\mathrm{NEG}}}\right) & , \quad \text{if } z < -3 \end{cases} \quad \text{where,}$$

$\mathrm{SD}_{3\mathrm{POS}}$ and $\mathrm{SD}_{3\mathrm{NEG}}$ are the cut-off 3 SD and -3 SD, respectively, calculated by the LMS methods:

$$\mathrm{SD}_{3\mathrm{POS}} = M[1 + 3LS]^{\frac{1}{L}}$$

$$\mathrm{SD}_{3\mathrm{NEG}} = M[1 - 3LS]^{\frac{1}{L}}$$

$\mathrm{SD}_{23\mathrm{POS}}$ and $\mathrm{SD}_{23\mathrm{NEG}}$ are the difference between the cut-offs (3 SD and 2 SD) and (-2 SD and -3 SD), respectively, calculated by the LMS methods:

$$\mathrm{SD}_{23\mathrm{POS}} = M[1 + 3LS]^{\frac{1}{L}} - M[1 + 2LS]^{\frac{1}{L}}$$

$$\mathrm{SD}_{23\mathrm{NEG}} = M[1 - 2LS]^{\frac{1}{L}} - M[1 - 3LS]^{\frac{1}{L}}$$

References

Schumacher, D. (2020). anthro: Computation of the WHO Child Growth Standards. R package version 0.9.4. Retrieved from https://CRAN.R-project.org/package=anthro

World Health Organization. (2006). WHO Child Growth Standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Retrieved from https://www.who.int/childgrowth/standards/Technical_report.pdf