VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX16-809-121 Version 4.0 (Part 1 and Final Analysis)

An Exploratory Phase 2, 2-part, Randomized, Double-blind, Placebo-controlled Study with a Long-term, Open-label Period to Explore the Impact of Lumacaftor/Ivacaftor on Disease Progression in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for *F508del*

Authors of SAP: [redacted]

Version: 1.0
Version Date of SAP: 16 October 2020

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, Massachusetts 02210-1862

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[redacted]

3 INTRODUCTION

This statistical analysis plan (SAP) for the Part 1 (interim) and final analysis is based on the most recent approved clinical study protocol (CSP), electronic case report form (eCRF), and eCRF completion guidelines.

This SAP (Methods) documents the planned statistical analyses of efficacy and safety endpoints for the Part 1 analysis and the final analysis (FA), which have been pre-defined in the VX16-809-121 study protocol. It also documents analyses for [redacted] safety variables not specified in the protocol, which will provide supportive information for the scientific understanding of the drug entity.

The Vertex Biometrics Department will perform the statistical analysis of the efficacy and safety data; SAS (Version 9.4 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the Part 1 analysis data-cut and treatment unblinding for the Part 1 analysis. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP prior to the clinical database lock for the final analysis. Any changes made to the SAP (Methods) after the clinical database lock has occurred will be documented in the clinical study report for this study.

4 STUDY OBJECTIVES

4.1 Primary Objective

To explore the impact of Lumacaftor/ivacaftor (LUM/IVA) on disease progression in subjects aged 2 through 5 years with CF, homozygous for *F508del*.

4.2 Secondary Objectives

To explore the relationship between lung clearance index (LCI) and imaging modalities for LUM/IVA in subjects aged 2 through 5 years with CF, homozygous for *F508del.*

5 STUDY ENDPOINTS

5.1 Efficacy Endpoints for Part 1 Analysis

5.1.1 Primary Endpoint

- Absolute change from baseline in magnetic resonance imaging (MRI) global chest score at Week 48

5.1.2 Secondary Endpoints

- Absolute change from baseline in LCI2.5 through Week 48
- Absolute change from baseline in weight-for-age z-score at Week 48
- Absolute change from baseline in stature-for-age z-score at Week 48
- Absolute change from baseline in body mass index (BMI)-for-age z-score at Week 48

[redacted]

[redacted]

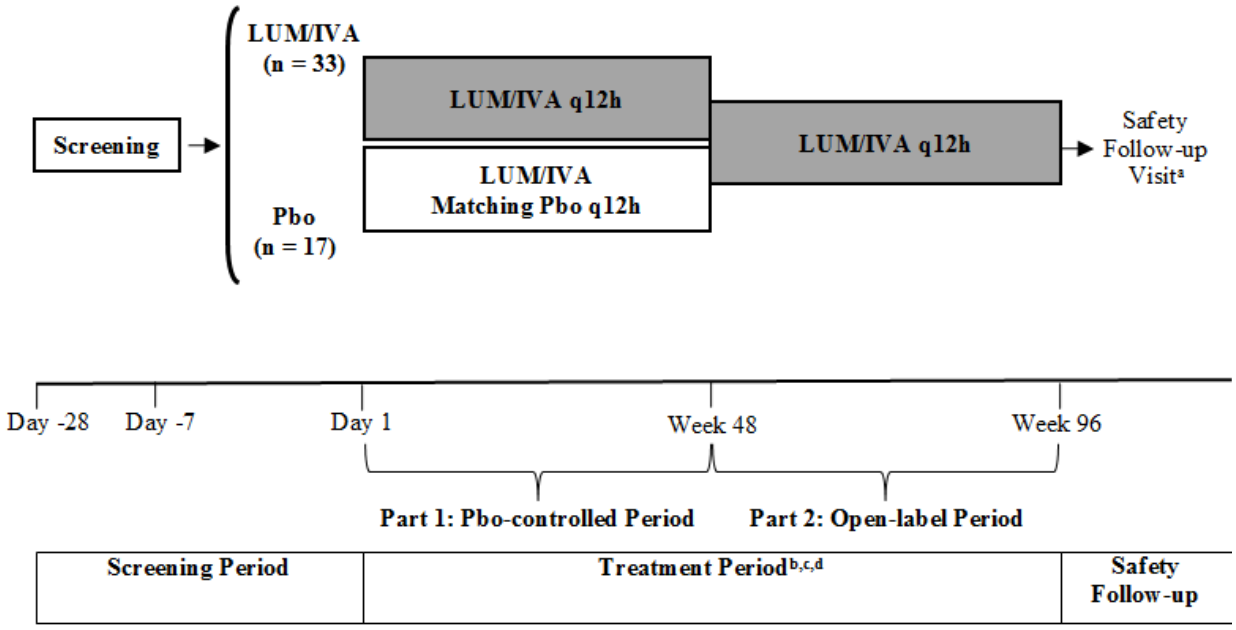
[redacted]

6 STUDY DESIGN

6.1 Overall Design

This is a Phase 2, 2-part, randomized, double-blind, placebo-controlled, parallel-group study with a long-term open-label period in subjects 2 through 5 years of age with CF, homozygous for *F508del*. A schematic of the study design is shown in Figure 6-1.

Figure 6-1 Schematic of the Study Design



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

[a] The Safety Follow-up Visit is scheduled to occur 2 weeks (± 4 days) after the last dose. The Safety Follow-up Visit is required for 1) subjects who complete their ETT Visit <10 days after the last dose of study drug and 2) subjects who interrupt study drug treatment and complete their Week 96 Visit <10 days after the last dose of study drug; it is not required for subjects who continue onto commercially-available, physician-prescribed study drug within 2 weeks (± 4 days) of completing study drug treatment at the Week 96 or ETT Visit.

[b] Approximately 50 subjects are planned to be randomized (2:1) to receive LUM/IVA or placebo. Subjects will receive LUM 100 mg/IVA 125 mg every 12 hours (q12h) (subjects weighing <14 kg at screening), LUM 150 mg/IVA 188 mg q12h (subjects weighing ≥14 kg at screening), or matching placebo (Part 1 only) during the Treatment Period.

[c] No downward dose adjustments will be made if a subject's weight decreases. If a subject subsequently weighs ≥14 kg at 2 consecutive visits, the dose will be adjusted to LUM 150 mg/IVA 188 mg q12h, at the second visit where weight ≥14 kg. Subjects who turn 6 years of age at or after the Week 48 Visit will receive LUM 200 mg/IVA 250 mg q12h (starting at the Week 48 Visit or the next scheduled visit after turning 6 years of age), regardless of weight.

[d] Subjects who prematurely discontinue study treatment will have an ETT Visit as soon as possible.

In Part 1, subjects will be randomized 2:1 to receive LUM/IVA or placebo. The dose regimens of LUM 100 mg/IVA 125 mg q12h (subjects weighing <14 kg at screening) and LUM 150 mg/IVA 188 mg q12h (subjects weighing ≥14 kg at screening) were chosen as shown in Table 6-1. If a subject weigh is ≥14 kg at 2 consecutive visits, the dose will be adjusted to LUM 150 mg/IVA 188 mg q12h at the second visit where weight is ≥ 14 kg. After completing Part 1, all subjects who continue to participate the open-label Part 2 will receive LUM/IVA with the planned dosages. Subjects who turn 6 years of age at or after the Week 48 Visit will receive LUM 200 mg/IVA 250 mg q12h (starting at the Week 48 Visit or the next scheduled visit after turning 6 years of age), regardless of weight.

Table 6-1 Treatment Arms and Planned Dosages

Treatment Arm	LUM Dose	IVA Dose
LUM/IVA (Weight at Screening <14 kg)	100 mg q12h	125 mg q12h
LUM/IVA (Weight at Screening ≥14 kg)	150 mg q12h	188 mg q12h
Matching Placebo	0 mg	0 mg
LUM/IVA (Age ≥6 years at or after Week 48 Visit)	200 mg q12h	250 mg q12h

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

6.2 Sample Size and Power

The proposed sample size of 50 subjects (2:1 randomization: 33 LUM/IVA subjects and 17 placebo subjects) is based on the number of potential subjects expected to be available for participation. No formal sample size calculation was conducted.

6.3 Randomization

Study Part 1

The proposed sample size of 50 subjects will be randomized by 2:1 ratio to the LUM/IVA arm or placebo arm.

An interactive web or voice response system (IXRS) will be used to assign subjects to treatment or placebo. The randomization code will be produced by Vertex Biostatistics or a qualified randomization vendor.

Study Part 2

Part 2 is an open-label extension period. Randomization is not applicable.

6.4 Blinding and Unblinding

Refer to the CSP Section 10.7 for details.

6.5 Part 1 and Final Analysis

Part 1 analysis will be conducted after all subjects have completed Part 1 (i.e., up to and including the Week 48 Visit) or have prematurely discontinued. The final analysis will occur after all subjects have completed the study or have prematurely discontinued.

7 ANALYSIS SETS

The following analysis sets are defined: All Subjects Set, Full Analysis Set, [redacted] and Safety Set.

A summary of analysis sets is presented in Table 7-1.

Table 7-1 Summary of Analysis Sets

Analysis Set	Target Analyses	Treatment Group/Sequence
All Subject Set[a]	Individual subject listing and disposition summary for Part 1 analysis	• LUM/IVA • PBO
Full Analysis Set (FAS)[a]	Efficacy and baseline demographic for Part 1 analysis	• LUM/IVA • PBO
	By-visit efficacy summary for FA	• LUM/IVA→LUM/IVA • PBO→LUM/IVA

[redacted]		
Safety Set[b]	Safety for Part 1 analysis	• LUM/IVA • PBO
	Part 2 safety analysis, individual subject listing, and disposition summary for FA	• Overall LUM/IVA OR • LUM/IVA→LUM/IVA • PBO→LUM/IVA

[a] Treatment label is based on the treatment the subject was randomly assigned to in the study Part 1 or the corresponding treatment sequence from Part 1 to Part 2.
[b] Treatment label is based on the treatment that the subject received in the study Part 1 or its corresponding treatment sequence from Part 1 to Part 2.
FA: final analysis; IVA: ivacaftor; LUM: lumacaftor; PBO: placebo

7.1 All Subjects Set

The **All Subjects Set** will include all subjects who are randomized or receive at least 1 dose of study drug. This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

7.2 Full Analysis Set

The **Full Analysis Set** (FAS) will include all randomized subjects who carry the intended CFTR allele mutation and receive at least 1 dose of study drug in the study Part 1. The FAS will be used to summarize subject demographics and baseline characteristics, and for all efficacy analyses, unless otherwise specified.

[redacted]

7.4 Safety Set

The **Safety Set** will include all subjects who receive at least 1 dose of study drug. The Safety Set will be used for all safety analyses.

8 ANALYSIS PERIOD

The analysis period used for efficacy and safety endpoints in the Part 1 Analysis or FA is described below.

8.1 Part 1 Efficacy Analysis Period

The **Part 1 Efficacy Analysis Period** will include the time from the first dose date of study drug until the last efficacy assessment in Part 1, which may be collected up to the Week 48 Visit.

8.2 Part 1 Treatment-Emergent Period

The **Part 1 Treatment-Emergent (TE) Period** will include the time from the first dose of study drug (including the matched placebo) until 14 days after the last dose of study drug of Part 1 or the completion of study participation of Part 1, whichever occurs first.

Completion of study participation of Part 1 is defined as the following:

- For subjects who complete Part 1 and enter Part 2: the day prior to the first dose of study drug of Part 2
- For subjects who prematurely discontinue study drug treatment during the Part 1 treatment period but do not withdraw consent (and assent, as applicable): the latest of the Week 48 Visit, ETT or Safety Follow-up Visit (if required)
- For subjects who withdraw consent or assent: date of withdrawal of consent or assent, whichever is earlier.

[redacted]

8.4 Part 2 Safety Period

The **Part 2 Safety Period** will include the time from the first dose of study drug of Part 2 until 14 days after the last dose of LUM/IVA or the completion of study participation, whichever occurs first.

Completion of study participation is defined as:

- For subjects who complete the study, the latest of the ETT Visit or Safety Follow-up Visit (if required).
- For subjects who prematurely discontinue study drug treatment during the study but do not withdraw consent (and assent, as applicable): the latest of ETT or Safety Follow-up Visit (if required).
- For subjects who withdraw consent or assent: date of withdrawal of consent or assent, whichever is earlier.

The Part 2 Safety Period will be used for analysis of safety data in the FA.

9 STATISTICAL ANALYSIS

9.1 General Considerations

As summarized in Table 7-1, the 2 treatment groups in Part 1 are

- LUM/IVA
- Placebo (PBO)

and the 2 treatment sequences from Part 1 to Part 2 are as follows:

- LUM/IVA → LUM/IVA
- PBO → LUM/IVA

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

Categorical variables will be summarized using counts and percentages.

Unless otherwise specified,

- the **Study Baseline** value is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug (including the matched placebo). The study baseline will be used to calculate the absolute and relative change from baseline for efficacy analyses, unless otherwise specified.
- the **LUM/IVA Baseline** value is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug of Part 1 if the subject actually received at least one dose of LUM/IVA in Part 1, or before the first dose of study drug of Part 2 if the subject did not actually receive at least one dose of LUM/IVA in Part 1. The LUM/IVA baseline will be used to calculate the change from baseline in safety analysis in the FA, unless otherwise specified.

Absolute change from baseline will be calculated as post-baseline value – baseline value.

Relative change from baseline will be calculated as (post-baseline value – baseline value)/baseline value.

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

1) In scheduled visit windows per specified visit windowing rules
2) In the derivation of baseline and last on-treatment measurements
3) In the derivation of maximum and minimum values, and maximum and minimum change from baseline values during analysis period for safety analyses
4) In individual subject data listings as appropriate

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix A.

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.

9.2 Part 1 Analysis

The Part 1 analysis will be conducted after all subjects have completed the study Part 1 or have discontinued prematurely. The efficacy analysis and safety analysis will be based on the efficacy and safety data from study Part 1 only.

9.2.1 Background Characteristics

9.2.1.1 Subject Disposition

A disposition table will be provided for Part 1 with the number of subjects in:

- All Subjects Set

- Randomized
- Randomized but not dosed
- Full Analysis Set
- Safety Set

The number and percentage (based on the FAS) of subjects in each of the following disposition categories will be summarized by treatment group and overall:

- Completed Part 1 treatment
- Prematurely discontinued Part 1 treatment and the reason for discontinuation
- Completed Part 1 study participation
- Prematurely discontinued Part 1 study participation and the reason for discontinuation
- Continued to study Part 2

A listing will be provided for subjects who discontinued treatment or who discontinued study participation with reasons for discontinuation during Part 1.

9.2.1.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics at study baseline will be summarized based on the FAS and presented by treatment group and overall.

Demographic data will include the following:

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

Baseline characteristics will include the following:

- Weight (kg)
- Weight group (<14 kg and ≥14 kg)
- Weight-for-age z-score
- Stature (cm)
- Stature-for-age z-score
- BMI (kg/m^2)
- BMI-for-age z-score

Disease characteristics will include the following:

- $LCI_{2.5}$ at baseline

[redacted]

- MRI global chest score at baseline

[redacted]

In addition, data listings will also be provided for:

- Informed consent;
- Inclusion/Exclusion criteria violation for subjects with any such violations.

9.2.1.3 Medical History

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). For the FAS, medical history will be summarized descriptively by system organ class (SOC) and preferred term (PT). The corresponding data listing will also be provided.

9.2.1.4 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) and categorized as follows:

Prior medication: any medication that was administered during the 28 days before the first dose of study drug (including the matched placebo) in the treatment period.

Concomitant medication during the Part 1 TE period: medication continued or newly received during the Part 1 TE period.

A given medication may be classified as follows: prior, concomitant, and both prior and concomitant.

If a medication has a completely missing or partially missing start/end date and it cannot be determined whether it was taken before the first dose date of study drug, concomitantly during the Part 1 TE period, or after the Part 1 TE period, it will be considered as prior and concomitant. Details for imputing missing or partial start and/or stop dates of medication are described in **Appendix B**.

For FAS, prior medications and concomitant medications during the Part 1 TE period will be summarized descriptively by:

1) treatment group and overall, preferred name (PN)
2) treatment group and overall, anatomic class (ATC) level 1, ATC level 2, and PN

9.2.1.5 Study Drug Exposure

Study drug exposure summaries will be based on the Safety Set for the study Part 1 and presented by treatment group.

Duration of study drug exposure is defined as last dose date of Part 1 – first dose date of Part 1 + 1 day, regardless of any interruptions in dosing.

Duration of study drug exposure period (in weeks) will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized as a categorical variable by intervals using counts and percentages.

9.2.1.6 Study Drug Compliance

Percentage of study drug compliance during the study Part 1 will be summarized descriptively based on the FAS and will be presented by treatment group and overall.

Study drug compliance will be calculated as: $100 \times (1 -$ [total number of days of study drug interrupted prior to the date of last dose in Part 1] / [duration of drug exposure in Part 1]). A study drug interruption on a given day is defined as an interruption of any study drug on that day. A study drug interruption that continues through the end of the study participation (i.e., subject does not resume study drug before the end of the study participation) will not be included in the compliance calculation.

Descriptive summary statistics include number of subjects (n), mean, SD, median, min, and max. It will also be summarized in categories: <80% and ⩾80% using frequency tables.

In addition, percentage of stick packs taken will be calculated using the following formula: 100 x [(total number of stick packs dispensed during Part 1) – (total number of stick packs returned during Part 1)] / (total number of stick packs planned to be taken per day during Part 1 x duration of Part 1 drug exposure in days). Summary similar to those for the study drug compliance will be produced based on the FAS.

9.2.1.7 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. IPD rules will be developed and finalized before database cut/lock.

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

- Subject was enrolled in the study despite the violation of inclusion/exclusion criteria
- Subject was less than 80% compliant with study drug for non-safety reasons
- Subject received prohibited concomitant medications
- Subject received the wrong treatment or incorrect doses
- Subject remained in the study despite meeting withdrawal criteria

Occurrence of any of these events should be considered as potential IPDs, but a blinded team should categorize them as IPDs only if they have the potential to significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

IPDs (from the clinical database or from the site deviation log) will be summarized descriptively based on the FAS and presented by treatment group and overall. Additionally, IPDs will be provided in an individual subject data listing.

9.2.2 Efficacy Analysis

Unless otherwise specified, all efficacy analyses described in this section will be based on the FAS and presented by treatment group. The study baseline will be used to calculate the change from baseline for continuous efficacy endpoints.

9.2.2.1 Analysis of Primary Variable

9.2.2.1.1 Definition of Variable

The primary efficacy variable is the absolute change from baseline in MRI global chest score at Week 48.

MRI Chest Scores: MRI scans will be assessed semi-quantitatively via a standardized chest MRI scoring system[8,9]. Each subject will have 6 lobes scored with the lingula treated as a separate lobe. The scoring parameters, score aggregation, and global score calculations are described as below.

After scans are reviewed, MRI scores will be captured using the following 7 scoring parameters for each of the 6 lobes:

1. Bronchiectasis / Wall thickening
2. Mucus plugging
3. Abscesses / Sacculations
4. Consolidations
5. Special findings
6. Mosaic pattern
7. Perfusion abnormalities

Scores assigned to each parameter:

- 0 = normal
- 1 = < 50% of lobe involved
- 2 = ≥ 50% of lobe involved

[redacted]

The primary variable of MRI Global Chest Score is defined as:

- MRI Global Score = Sum of parameters 1 – 7

9.2.2.1.2 Primary Analysis

The primary analysis will be performed using Bayesian methods. Specifically, the actual Bayesian posterior probability of LUM/IVA being superior to Placebo in the MRI global chest score at Week 48 will be calculated using a vague normal prior distribution. Bayesian summary statistics including the Bayesian posterior mean difference and corresponding 95% credible intervals will also be provided.

In addition, descriptive summary statistics for both between treatment arm difference and within-treatment change at Week 48 will be presented. Descriptive summary statistics including number of subjects (n), mean, median, SD, minimum, and maximum, along with the corresponding 95% CIs will be provided.

9.2.2.2 Analysis of Secondary Variables

9.2.2.2.1 Definition of Variables

Lung clearance index (LCI): LCI assessments are derived from N2-multiple-breath washout (MBW) testing. $LCI_{2.5}$ represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value, [redacted] Refer to Section 11.4.2 of the CSP for details.

Body mass index (BMI): the BMI at each visit is calculated using the weight and height at each visit as follows:

$$BMI = \text{Weight (kg)} / [\text{Height (m)}]^2$$

BMI z-score: the BMI score, adjusted for age and sex, will be referred to as BMI-for-age z-score (BMI z-score). The BMI z-score will be calculated by using Centers for Disease Control and Prevention (CDC) growth charts[7], with the age (in months) used for the calculation defined in Appendix A.

Stature z-score: stature, adjusted for age and sex, will be referred to as stature-for-age z-score (stature z-score). The calculation of stature z-score is similar to that of BMI z-score.
Weight z-score: weight, adjusted for age and sex, will be referred to as weight-for-age z-score (weight z-score). The calculation of weight z-score will be exactly the same as stature z-score.

9.2.2.2.2 Analysis Method

Both within-treatment arm change and between treatment arm difference will be analyzed for secondary variables, subject to the considerations described below.

Absolute change from baseline in $LCI_{2.5}$ through Week 48:

Analysis of within-treatment arm change will be based on descriptive summary statistics. The change from baseline to the average of all post-baseline measures at scheduled visits through Week 48 (defined as the average of Week 12, 24, 36, 48) will be used for this analysis. Descriptive summary statistics include number of subjects (n), mean, median, SD, minimum, and maximum, along with the corresponding 95% CIs will be provided.

If the LUM/IVA treatment group or the placebo group demonstrates a within-treatment arm change with 95% CI excluding 0, and the variability of this variable is within expectation, the analysis of between-treatment difference may also be performed based on the descriptive summary statistics with the corresponding 95% CIs.

In addition, the summary of raw values and the absolute change from baseline at each post-baseline visit up to Week 48 will be provided.

Absolute change in Weight z-score from baseline at Week 48:

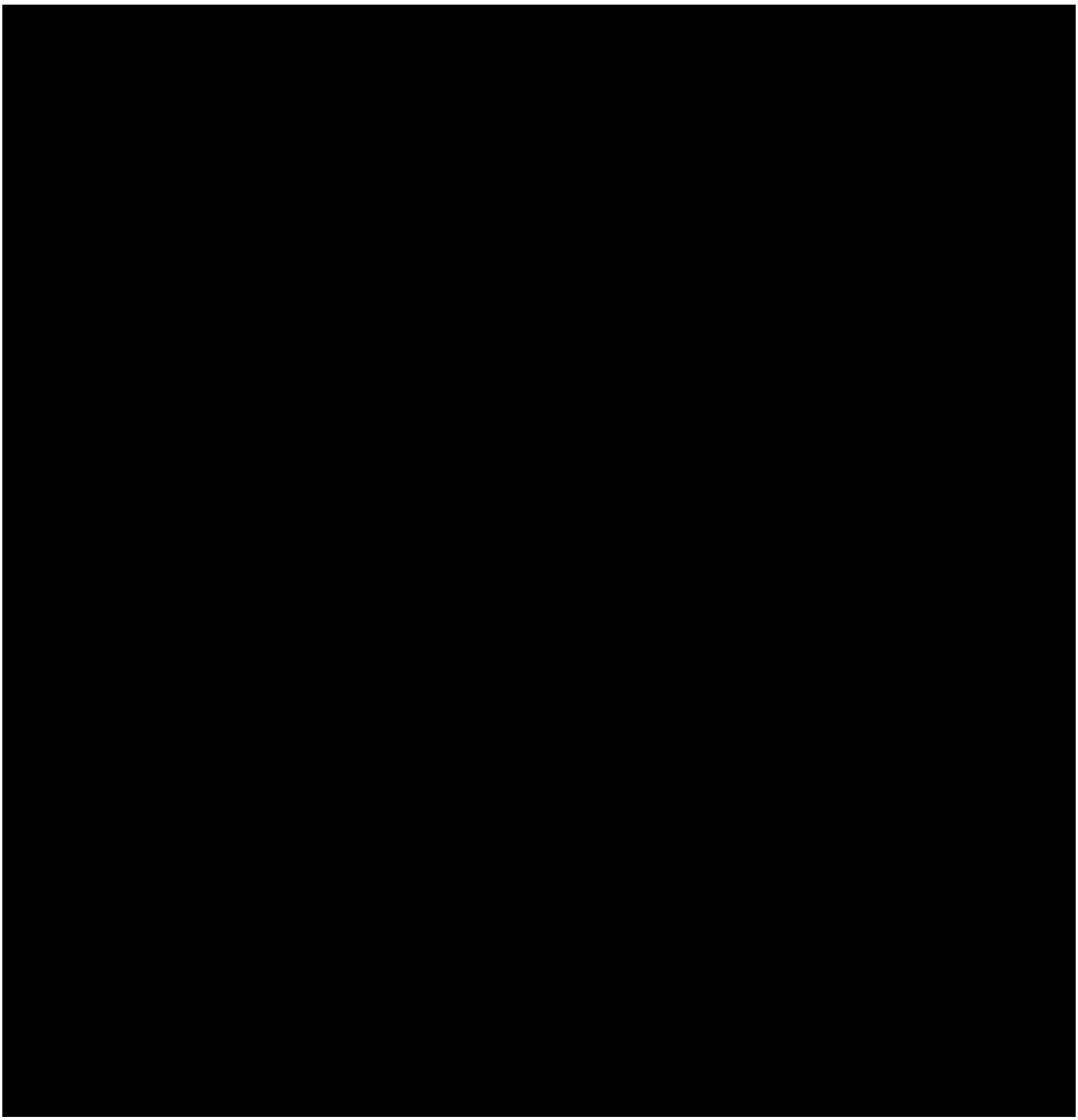
Absolute change in Stature z-score from baseline at Week 48;

Absolute change in BMI z-score from baseline at Week 48;

Analyses of within-treatment arm change will be based on descriptive summary statistics. The change from baseline at Week 48 will be used for this analysis. Descriptive summary statistics including number of subjects (n), mean, median, SD, minimum, and maximum, along with the corresponding 95% CIs will be provided.

If the LUM/IVA treatment group or the placebo group demonstrates a within-treatment arm change with 95% CI excluding 0, and the variability of this variable is within expectation, the analysis of between-treatment difference may also be performed based on the descriptive summary statistics with the corresponding 95% CIs.

Additional summary of raw values and absolute changes from baseline at each post-baseline visit up to Week 48 will also be provided.



[redacted]

[redacted]

9.2.3 Safety Analysis

Unless otherwise specified, all safety analyses of Part 1 analysis will be based on data from the Part 1 TE period for all subjects in the Safety Set. Subjects will be analyzed according to the treatment they actually received in the study Part 1. For subjects who have received study drug from more than one treatment, i.e. received both LUM/IVA and Placebo study drug, the treatment group allocation will be the LUM/IVA.

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

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values
- Vital signs
- Ophthalmologic examinations (OEs)
- Physical examinations (PEs)

Only descriptive analysis will be performed for safety, and no confidence interval will be computed.

9.2.3.1 Adverse Events

For analysis purposes, AEs will be classified as pre-treatment AEs and TEAEs during the Part 1 TE Period in Part 1 analysis, defined as follows:

Pretreatment AE: any AE that occurred before the first dose date of study drug (including the matched placebo)

TEAE during the Part 1 TE Period: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug (including the matched placebo) through the end of the Part 1 TE period

For AEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs are pretreatment or post-treatment, the AEs will be classified as TEAEs.

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

An overview of all TEAEs during Part 1 TE period will be summarized by treatment group and overall in the following categories:

- Number of TEAEs
- Subjects with any TEAEs
- Subjects with TEAEs by strongest relationship
- Subjects with TEAEs by maximum severity
- Subjects with TEAEs leading to study drug discontinuation
- Subjects with TEAEs leading to study drug interruption
- Subjects with related TEAEs
- Subjects with serious TEAEs
- Subjects with TEAE leading to death

The following summary tables of TEAEs during Part 1 TE period 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), and by treatment group:

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Related TEAEs
- Serious TEAEs
- TEAEs leading to death

When summarizing the number and percentages of subjects, subjects with multiple occurrences of the same adverse event or a continuing adverse event will be counted once, and only the maximum severity level will be presented in the severity summaries, and the strongest relationship level in the relationship summaries.

All AEs, including pretreatment AEs and TEAEs during the Part 1 TE period will be presented in an individual subject data listing based on the All Subjects Set. In addition, separate listings containing individual subject adverse event data for TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, SAEs and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.

The AEs of special interest (AESI) of elevated transaminases and respiratory event are defined as the following.

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 event AESI

The respiratory event AESI 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 be summarized by treatment group in the following categories:

- Subjects with events
- Subjects with events by maximum severity
- Subjects with events leading to treatment discontinuation
- Subjects with events leading to treatment interruption
- Subjects with serious events
- Subjects with events leading to death
- Duration of events
- Time-to-onset of first event

9.2.3.2 Clinical Laboratory

For the treatment-emergent laboratory assessments during the Part 1 TE period, the observed values and change from study baseline of the continuous hematology and chemistry results will be summarized in SI units at each visit by treatment group.

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the Part 1 TE period will be summarized by treatment group. The threshold analysis criteria are provided in Appendix D.

In addition, a listing containing individual subject hematology and chemistry values during the Part 1 TE period will be provided with a column indicating outside reference range or not. This listing will include data from both scheduled and unscheduled visits.

9.2.3.3 Vital Signs

For the treatment-emergent vital signs measurements during the Part 1 TE period, the observed values and change from study baseline will be summarized at each visit by treatment group. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute).

In addition, a listing containing individual subject vital signs values during the Part 1 TE period will be provided. This listing will include data from both scheduled and unscheduled visits.

9.2.3.4 Ophthalmologic Examination

The OE results during Part 1 TE period will be presented in individual subject data listings.

9.2.3.5 Physical Examination

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

9.3 Final Analyses

The final analysis will be conducted after all subjects have completed the study or have prematurely discontinued.

9.3.1 Background Characteristics

9.3.1.1 Subject Disposition

A disposition table will be provided for the study Part 2 with the number of subjects in:

- FAS, Part 2 (dosed during the study Part 2)
- Safety Set, Part 2 (dosed during the study Part 2)

The number and percentage (based on the FAS, Part 2) of subjects in each of the following disposition categories will be summarized for the study Part 2 by treatment sequence from Part 1 to Part 2:

- Completed Part 2 treatment
- Completed study
- Prematurely discontinued treatment during Part 2 and the reason for discontinuation

- Prematurely discontinued study participation during Part 2 and the reason for discontinuation

A listing will be provided for subjects who discontinued treatment or who discontinued study with reasons for discontinuation during Part 2.

9.3.1.2 Study Drug Exposure

Duration of study drug exposure on LUM/IVA during the study Part 2 is defined as last LUM/IVA dose date of Part 2 – first LUM/IVA dose date of Part 2 + 1 day, regardless of any interruptions in dosing.

Duration of study drug exposure on LUM/IVA during the Part 2 Safety Period (in weeks) will be summarized descriptively based on the Safety Set, Part 2 for overall LUM/IVA treatment group by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized as a categorical variable by intervals using counts and percentages.

9.3.1.3 Study Drug Compliance

Percentage of study drug compliance during the study Part 2 will be summarized descriptively based on the FAS, Part 2 and presented by overall LUM/IVA treatment group.

Study drug compliance will be calculated as: 100 × (1 − [total number of days of LUM/IVA interrupted prior to the date of last dose of LUM/IVA in Part 2] / [duration of LUM/IVA exposure in Part 2]). A study drug interruption on a given day is defined as an interruption of any study drug on that day. A study drug interruption that continues through the end of the study participation (i.e., subject does not resume study drug before the end of the study participation) will not be included in the compliance calculation.

Descriptive summary statistics include the number of subjects (n), mean, SD, median, min, and max. It will also be summarized in categories: <80% and ≥80% using frequency tables. A listing containing subjects with study drug interruptions will be provided.

In addition, percentage of stick packs/tablets taken will be calculated using the following formula: 100 x [(total number of stick packs/tablets dispensed during Part 2) – (total number of stick packs/tablets returned during Part 2)] / (total number of stick packs/tablets planned to be taken per day during Part 2 x duration of Part 2 drug exposure in days). Summary similar to those for the study drug compliance will be produced based on the FAS, Part 2.

9.3.1.4 Important Protocol Deviations

IPDs (from the clinical database or from the site deviation log) during Part 2 will be summarized descriptively based on the FAS, Part 2 and presented by treatment sequence from Part 1 to Part 2. Additionally, IPDs will be provided in an individual subject data listing.

[redacted]

[redacted]

[redacted]

9.3.3 Safety Analysis

Safety analyses specified for the Part 1 analysis (Section 9.2.3) will be performed similarly for the Part 2 Safety Period based on the Safety Set, Part 2 in FA.

Unless otherwise specified, analyses of adverse events and threshold analysis for clinical laboratory and vital signs will be summarized for the Part 2 Safety Period and presented for overall LUM/IVA treatment group. Analyses on change from LUM/IVA baseline of clinical laboratory and vital signs will be summarized at each Part 2 visit and presented by treatment sequence from Part 1 to Part 2.

9.3.3.1 Adverse Events

For analysis purpose, AEs in FA will be classified as TEAE during the Part 2 Safety Period and Post-treatment AEs, defined as follows:

TEAE during the Part 2 safety period: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug in Part 2 through the end of the Part 2 Safety Period.

Post-treatment AE: any AE that worsened (either in severity or seriousness) or that was newly developed after the Part 1 TE period if subjects who did not receive study drug in Part 2 or after the Part 2 Safety Period if subjects received study drug in Part 2.

For the overview of all TEAEs during the Part 2 Safety Period (as defined in Section 9.2.3.1), the frequency counts and percentages will be summarized.

For the summary tables of TEAEs during the Part 2 Safety Period, the frequency counts and percentages will be presented by MedDRA SOC and PT.

In addition, TEAEs during the Part 2 Safety Period and post-treatment AEs will be presented in an individual subject data listing based on the Safety Set, Part 2.

Similar as the Part 1 analysis of AESIs, the treatment-emergent elevated transaminases events and respiratory events during the Part 2 Safety Period will be summarized.

9.3.3.2 Clinical Laboratory and Vital Signs

For the treatment-emergent laboratory and vital sign assessments during the Part 2 Safety Period, the observed values and change from the LUM/IVA baseline values will be summarized at each Part 2 visit and presented by treatment sequence.

For the treatment-emergent clinical laboratory, the number and percentage of subjects meeting at least 1 threshold analysis criterion during the Part 2 Safety Period will be summarized. The threshold analysis criteria are provided in Appendix D.

In addition, a listing containing individual subject hematology and chemistry values and a listing containing individual subject vital signs values during the study Part 2 will be provided. Both listings will include data from both scheduled and unscheduled visits.

9.3.3.3 Ophthalmologic Examination

The OE results during the Part 2 Safety Period will be presented in individual subject data listings.

9.3.3.4 Physical Examination

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

[redacted]

10 DMC ANALYSIS

An independent data monitoring committee (DMC) was formed before initiation of this study. The DMC's objectives and operational details are described in a separate document (DMC Charter) which was finalized before the first subject was screened in the study. The DMC will conduct planned safety reviews of study data as outlined in the DMC Charter and DMC Statistical Analysis Plan.

11 REFERENCES

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12 LIST OF APPENDICES

Appendix A: Analysis Visit Windows for Safety and Efficacy Assessment

Table 12-1 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window[2,3,4,5] (in study Part 1 or 2 days)
Safety Assessment			
Serum Chemistry	Day 1 (Study Baseline) Day 15 Week 12 Week 24 Week 36 Week 48	1 15 85 169 253 337	≤1 Pre-dose [1, 49] [50, 126] [127, 210] [211, 294] [295, min(337+67, 1st dose of Part 2)]
	Day 350 Week 60 Week 72 Week 84 Week 96 Safety Follow-up	Part 2 Day 15 Part 2 Day 85 Part 2 Day 169 Part 2 Day 253 Part 2 Day 337 N/A	[1st dose of Part 2, 49] [50, 126] [127, 210] [211, 294] [295, 337+67] Use nominal visit
Hematology	Day 1 (Study Baseline) Week 12 Week 24 Week 36 Week 48	1 85 169 253 337	≤1 Pre-dose [1, 126] [127, 210] [211, 294] [295, min(337+67, 1st dose of Part 2)]
	Week 60 Week 72 Week 84 Week 96 Safety Follow-up	Part 2 Day 85 Part 2 Day 169 Part 2 Day 253 Part 2 Day 337 N/A	[1st dose of Part 2, 126] [127, 210] [211, 294] [295, 337+67] Use nominal visit
Vital signs (excluding Weight and Stature)	Day 1 (Study Baseline) Day 15 Week 12 Week 24 Week 36 Week 48	1 15 85 169 253 337	≤1 [1, 49] [50, 126] [127, 210] [211, 294] [295, min(337+67, 1st dose of Part 2)]
	Day 350 Week 60 Week 72 Week 84 Week 96 Safety Follow-up	Part 2 Day 15 Part 2 Day 85 Part 2 Day 169 Part 2 Day 253 Part 2 Day 337 N/A	[1st dose of Part 2, 49] [50, 126] [127, 210] [211, 294] [295, 337+67] Use nominal visit
Efficacy Assessment			

Table 12-1 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window[2,3,4,5] (in study Part 1 or 2 days)
MRI	Day 1 (Study Baseline) Week 48	1 337	≤1 Pre-dose (1, min(337+67, 1st dose of Part 2]
	Week 96	Part 2 Day 337	[1st dose of Part 2, 337+67]
MBW [redacted]	Day 1 (Study Baseline) Week 12 Week 24 Week 36 Week 48	1 85 169 253 337	≤1 Pre-dose (1, 126] [127, 210] [211, 294] [295, min(337+67, 1st dose of Part 2)]
	Week 60 Week 72 Week 84 Week 96	Part 2 Day 85 Part 2 Day 169 Part 2 Day 253 Part 2 Day 337	[1st dose of Part 2, 126] [127, 210] [211, 294] [295, 337+67]
Weight and Stature	Day 1 (Study Baseline) Day 15 Week 12 Week 24 Week 36 Week 48	1 15 85 169 253 337	≤1 Pre-dose [1, 49] [50, 126] [127, 210] [211, 294] [295, min(337+67, 1st dose of Part 2)]
	Day 350 Week 60 Week 72 Week 84 Week 96	Part 2 Day 15 Part 2 Day 85 Part 2 Day 169 Part 2 Day 253 Part 2 Day 337	[1st dose of Part 2, 49] [50, 126] [127, 210] [211, 294] [295, 337+67]
[redacted]			

Notes:
[1]Visit name for analysis purpose is used to report data in tables and figures.

[2] The analysis visit windows will be applied using the following rules for both scheduled and unscheduled visits:
a. If no numerical measurement is available within a visit window, the measurement will be considered missing for the visit.
b. If there is more than 1 numerical measurement available within a visit window, use the following rules:
   i. The measurement closest to the target day will be used; or
   ii. If there are multiple measurements with the same distance from the target day, the latest measurement will be used.

Table 12-1 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window[2,3,4,5] (in study Part 1 or 2 days)

[3] For lab and vital sign measurement collected on the date of first dose of study drug in Treatment Period (Part 1 or Part 2 of study), if it cannot be determined whether the measurement is before or after the first dose:

a. Scheduled measurement will be treated as pre-dose observation.
b. Unscheduled measurement will be treated as post-dose observation.

[4] For safety assessment, Safety Follow-up analysis visit will be based on nominal Safety Follow-up visit. If a subject doesn't have a nominal Safety Follow-up visit but has an ETT visit with study **day >680**, then the ETT visit will be mapped into Safety Follow-up analysis visit.

Derived Variables:

1. Age (in years) at first dose date and nominal visit (for demographics and listing variables):

   Obtain the age at informed consent (in days) in "yy, mm" format (e.g., 24 years, 6 months) from the Vital Signs (VS) page at the Screening Visit and add 0.5 month to convert to days.

   Obtain the informed consent date.

   Then age (in years) at first dose or nominal visit = [(first dose date or nominal visit date – informed consent date) in days + age at informed consent (in days)]/365.25.

2. Age (in months) at nominal visit (for use in calculation of BMI, stature z-score, and weight z-score):

   Obtain the age at informed consent (in months) in "yy, mm" format (e.g., 24 years, 6 months) from Vital Signs (VS) page at the Screening Visit.

   Obtain the informed consent date.

   Then age (in months) at nominal visit = integer part of {[(age at informed consent (in months) + 0.5 + diff(first dose date or nominal visit date, informed consent date) in months]} + 0.5.

3. Missing first dose date or last dose date

   If the first dose date is missing, use Day 1 visit date to impute.

   If the last dose date is missing or partial date is reported, the last dose date will be imputed based on, in descending order priority, the Early Treatment Termination (ETT) visit date, last visit date before the Safety Follow-up, or the last study drug administration date from EX SDTM domain, as appropriate. The imputation algorithm will ensure the imputed last dose date does not exceed the study participation end date.

[redacted]

5. The 1st dose of Part 2:

   The analysis visit window of the study Part 1 is ended at the day of Week 48 visit before the 1st dose of Part 2. The analysis visit window of the study Part 2 is started from the day of Week 48 visit after the 1st dose of Part 2.

6. Post-dose Vital signs:

   The analysis window for post-dose vital sign measures will be1 hour (± 15 minutes), 2 hours (± 15 minutes), and 4 hours (± 15 minutes). Any measures after the last post-dose analysis window will be allocated to the next analysis window.

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

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

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date (in practical, use Jan. 01, 2000 to impute).
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 practical, use Dec. 31, 2050 to impute).

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

	Medication Stop Date	
Medication Start Date	**< First Dose Date of Study Drug**	**≥ First Dose Date and ≤ End Date of Part 1 TE Period**
< First dose date of study drug	P	PC
≥ First dose date and ≤ End date of Part 1 TE period	-	C

P: Prior; C: Concomitant during the Part 1 TE period

Imputation rules for missing and/or partial dates of non-pharmacological treatment/procedure will follow the same imputation rule.

Appendix C: Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined below. If the imputed AE start date is before the informed consent date, the AE start date will be imputed using the study informed consent date.

- **If only Day of AE start date is missing:**
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then
        - if AE start year and month are equal to the month and year of first dose date of the Treatment Period, then impute the AE start day as the day of first dose date of the Treatment Period;
        - else impute the AE start day as 1.
    - else impute the AE start day as 1.

  Compare the imputed AE start date with Part 1 TE period or cumulative safety period to determine whether the AE is pretreatment AE, TEAE during the Part 1 TE Period, TEAE during the Cumulative Safety Period, or post-treatment AE.

- **If Day and Month of AE start date are missing:**
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then
        - if AE start year is equal to the year of first dose date of the Treatment Period, then impute the AE start month and day as the month and day of first dose date of the Treatment Period;
        - else impute the AE start month as January and day as 1.
    - else impute the AE start month as January and day as 1.

  Compare the imputed AE start date with Part 1 TE period or cumulative safety period to determine whether the AE is pretreatment AE, TEAE during the Part 1 TE Period, TEAE during the Cumulative Safety Period, 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 and
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then impute the AE start date as the date of first dose date of the Treatment Period.
    - else impute AE date as the informed consent date.

The imputation should ensure the imputed AE start date is not before the informed consent date.

- Imputation rules for partial AE end date are defined below:

If partial end date, then impute as min (the last day of the month, end of study participation (of Part 1)) if day is missing, or min (Dec, end of study participation (of Part 1)) if month is missing.

Appendix D: Criteria for Threshold Analysis

Table 12-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Categorical change	Comments
Clinical Chemistry (LFT)		
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.
Direct Bilirubin	>ULN - ≤ 1.5xULN >1.5 – ≤ 2xULN >2 – ≤ 3xULN >3 – ≤ 10xULN >10xULN	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
GGT	>ULN - ≤ 2.5xULN >2.5 – ≤ 5.0xULN >5.0 – ≤ 20.0xULN >20.0xULN	CTCAE grade 1-4
Clinical Chemistry (Non-LFT)		
CPK (Creatine kinase)	>3x - ≤ 10xULN >10xULN	FDA criteria Feb 2005. Am J Cardiol April 2006.
Albumin	≤25 g/L	

Table 12-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Categorical change	Comments
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<85 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥150 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Amylase	>1x - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Lipase	>ULN - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.
Hematology		
WBC (Leukocytes)	<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 12-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Categorical change	Comments
Reticulocytes/Erythrocytes (%)	<LLN >ULN	No CTCAE