1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX19-445-116 Version 1.0 (Final Analysis)

A Phase 3b, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 6 Through 11 Years of Age Who Are Heterozygous for the *F508del* Mutation and a Minimal Function Mutation (F/MF)

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4 INTRODUCTION

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

This SAP (Methods) documents the planned statistical analyses of efficacy and safety endpoints defined in the VX19-445-116 study protocol. [redacted]

The Vertex Biometrics Department will perform the statistical analysis of 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 clinical database lock and treatment unblinding for the study. Any revisions to the approved SAP will be documented and approved in an amendment prior to the clinical database lock and treatment unblinding. Any changes made to the SAP (Methods) after the clinical database lock has occurred will be documented in the clinical study report for this study.

5 STUDY OBJECTIVES

5.1 Primary Objective

To evaluate the efficacy of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) in subjects 6 through 11 years of age with cystic fibrosis (CF), heterozygous for *F508del* and a minimal function (MF) mutation (F/MF).

5.2 Secondary Objectives

- To evaluate the pharmacodynamics (PD) of ELX/TEZ/IVA
- To evaluate the safety of ELX/TEZ/IVA

6 STUDY ENDPOINTS

6.1 Primary Endpoint

- Absolute change in lung clearance index2.5 ($LCI_{2.5}$) from baseline through Week 24

6.2 Secondary Endpoints

- Absolute change in sweat chloride (SwCl) from baseline through Week 24
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, standard 12-lead electrocardiograms (ECGs), vital signs, pulse oximetry

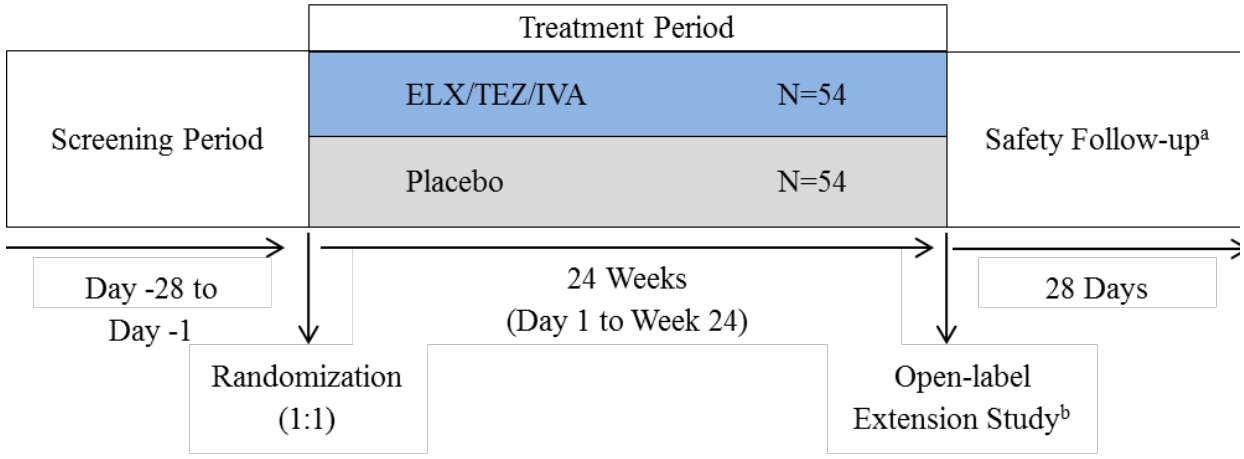
[redacted]

7 STUDY DESIGN

7.1 Overall Design

This is a Phase 3b, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in CF subjects aged 6 through 11 years who are heterozygous for the *F508del* mutation and a minimal function mutation (F/MF genotypes), as shown in Figure 7-1.

Figure 7-1 VX19-445-116 Study Design



ELX: elexacaftor; IVA: ivacaftor; N: number of subjects; TEZ: tezacaftor

[a] The Safety Follow-up Visit is scheduled to occur 28 days (± 7 days) after the last dose.

[b] Subjects who complete the visits in the Treatment Period, regardless of whether they are on a treatment interruption, will be offered the opportunity to enroll in an optional open-label extension safety study evaluating ELX/TEZ/IVA. The Safety Follow-up Visit is not required for subjects who complete the Week 24 Visit and have enrolled in an open-label study within 28 days after the last dose of study drug.

Approximately 108 subjects are planned to be randomized (1:1) to the ELX/TEZ/IVA group or the placebo group. Randomization will be stratified by $LCI_{2.5}$ determined at the Screening Visit (<10 versus ≥10) and weight at the Screening Visit (<30 kg versus ≥30 kg).

The planned dosages to be evaluated are shown in Table 7-1.

Table 7-1 Treatment Period Groups and Dosages

Treatment Group Weight at Screening Visit	**ELX Dosage**	**TEZ Dosage**	**IVA Dosage**
ELX/TEZ/IVA			
<30 kg	100 mg qd	50 mg qd	75 mg q12h
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
Placebo	0 mg	0 mg	0 mg

ELX: elexacaftor; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor

7.2 Sample Size and Power

Assuming a within-group SD of 1.5 and a treatment difference of -1.0 between ELX/TEZ/IVA and placebo, a sample size of 49 subjects completing the Treatment Period in each group for a total of 98 subjects will have approximately 90% power for the $LCI_{2.5}$ hypothesis testing, based on a 2-sided 2-sample t-test at a significance level of 0.05. Assuming a 10% dropout rate, approximately 108 subjects will be enrolled.

All power calculations were based on EAST software Version 6.4.

7.3 Randomization

Randomization will be stratified by $LCI_{2.5}$ determined at the Screening Visit (<10 versus ≥10) and weight at the Screening Visit (<30 kg versus ≥30 kg).

Randomization will occur before the first dose of study drug during the Treatment Period and may occur on either Day 1 or Day -1.

7.4 Blinding and Unblinding

Refer to the CSP Section 10.7 for details.

8 ANALYSIS SETS

The following analysis sets are defined: All Subjects Set, Full Analysis Set (FAS), and Safety Set.

8.1 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.

8.2 Full Analysis Set

The **FAS** will include all randomized subjects who carry the intended *CFTR* allele mutation and receive at least 1 dose of study drug. The FAS will be used to summarize subject demographics and baseline characteristics, and for all efficacy analyses in which subjects will be analyzed according to their randomized treatment group, unless otherwise specified.

8.3 Safety Set

The **Safety Set** will include all subjects who receive at least 1 dose of study drug. This safety set will be used for all safety analyses in which subjects will be analyzed according to the treatment they receive, unless otherwise specified.

9 STATISTICAL ANALYSIS

9.1 General Considerations

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.

Baseline value, unless otherwise specified, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the Treatment Period.

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.

Treatment-emergent (TE) Period will include the time from the first dose date of study drug to 28 days after the last dose of the study drug or to the date of completion of study participation, whichever occurs first.

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 during TE period, and maximum and minimum change from baseline values during TE 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 Background Characteristics

9.2.1 Subject Disposition

A disposition table will be provided 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 FAS) of subjects in each of the following disposition categories will be summarized by treatment group and overall:

- Completed treatment
- Prematurely discontinued treatment and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation
- Rollover to the open-label study

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

9.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics 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)
- 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, Other, and not collected per local regulations)
- Country

Baseline characteristics will include the following:

- Weight (kg)
- Weight z-score
- Height (cm)
- Height z-score
- BMI (kg/m^2)
- BMI z-score

Stratification categories will include the following:

- $LCI_{2.5}$ at the Screening Visit (<10 versus ≥10)
- Weight at the Screening Visit (<30 kg, and ≥30 kg)

Disease characteristics will include the following:

- $LCI_{2.5}$ at baseline (continuous)
- SwCl at baseline (continuous)

[redacted]

- Prior use of dornase alfa (Yes, No)
- Prior use of azithromycin (Yes, No)
- Prior use of inhaled antibiotic (Yes, No)
- Prior use of any bronchodilator (Yes, No)
- Prior use of any inhaled bronchodilator (Yes, No)
- Prior use of any inhaled hypertonic saline (Yes, No)
- Prior use of any inhaled corticosteroids (Yes, No)

In addition, data listings will also be provided for:

- Informed consent

- Inclusion/Exclusion criteria violation for subjects with any such violations

9.2.3 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.

9.2.4 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 56 days before the first dose of study drug.

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

Post-treatment medication: medication continued or newly received after the TE period.

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

If a medication has a missing or partially missing start/end date or time and if it cannot be determined whether it was taken before the first dose of study drug, concomitantly during the TE Period, or after the TE Period, it will be classified as prior, concomitant, and post treatment medication. 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 will be summarized descriptively using frequency tables by: 1) treatment group and overall, preferred name (PN); and 2) treatment group and overall, anatomic class (ATC) level 1, ATC level 2, and PN. Post-treatment medications will be also included in the medication listing.

9.2.5 Study Drug Exposure

Study drug exposure will be summarized based on the Safety Set and will be presented by treatment group.

Duration of study drug exposure (in weeks) will be calculated as: (last dose date of study drug – first dose date of study drug + 1)/7, regardless of study drug interruption.

Study drug exposure (in weeks) will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized by interval, using counts and percentages.

9.2.6 Study Drug Compliance

Study drug compliance will be summarized based on the FAS and will be presented by treatment group and overall.

Study drug compliance will be calculated as: 100 × [1 - (total number of days of study drug interruption) / (duration of study drug exposure in days)]. A study drug interruption on a given day is defined as an interruption of any study drugs 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.

Study drug compliance will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized in categories: <80% and ≥80% using frequency tables.

9.2.7 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 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

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.

9.3 Efficacy Analysis

Unless otherwise defined, all efficacy analyses described in this section will be based on the FAS.

9.3.1 Analysis of Primary Efficacy Endpoint

9.3.1.1 Definition of Variable

The primary efficacy endpoint is the absolute change in $LCI_{2.5}$ from baseline through Week 24.

Lung clearance index (LCI): the LCI assessments are derived from N_2-multiple-breath washout (MBW) testing. Each MBW will be performed in multiple replicates for each visit and the final LCI value will be calculated from the technically acceptable washout replicates as graded and determined by a central reader. The following algorithm is used to derive the valid LCI value at each visit based on the multiple attempt replicates:

- When there is only one acceptable replicate at the visit, the LCI values will not be calculated. The assessment for that subject at the corresponding visit will be missing.
- When there are 2 or more acceptable replicates at the visit, the mean of the values for the acceptable replicates will be calculated as the LCI value at the corresponding visit.

9.3.1.2 Primary Analysis

The primary analysis will be performed using a mixed-effects model for repeated measures (MMRM) with the absolute change from baseline at each post-baseline visit as the dependent variable. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects, with continuous baseline $LCI_{2.5}$ and weight at Screening (<30 versus ≥30 kg) as covariates. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the *F*-test for fixed effects will be estimated using the Kenward-Roger approximation[2]. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, a compound symmetry covariance structure will be used instead. Conditional on the observed data and covariates, missing data will be assumed to be missing at random and therefore will be handled by MMRM model.

The primary result obtained from the model will be the estimated treatment difference through Week 24 (defined as the average of Weeks 4, 8, 16, 24). Data obtained from Day 15, Week 4, Week 8, Week 16, and Week 24 Visits will be included in the model, but the Day 15 Visit will not be included in the estimation of the average treatment effect through Week 24. The least squares (LS) mean estimate with a 2-sided 95% CI and a 2-sided *P* value will be provided. The treatment difference at each post-baseline visit, obtained from the model, will also be provided.

The LS mean (with SE) obtained from the MMRM analysis at each post-baseline visit up to Week 24 will be plotted by treatment group. In addition, the post-baseline raw values and the absolute change from baseline at each post-baseline visit up to Week 24 will be summarized descriptively (n, mean, SD, median, minimum, and maximum).

9.3.2 Analysis of Secondary Endpoint

9.3.2.1 Definition of Variable

Sweat chloride (SwCl): the SwCl value for a given visit will be calculated as the mean of the non-missing sweat chloride measurements obtained on the left and right arms at that visit. If one of the two arm measurements at a time point is missing, the other will be used as the mean. A volume ≥15 µL is required for an accurate determination of sweat chloride. Any results reported as having volume <15 µL will be considered missing. Any sweat chloride values reported as <10 mmol/L or >160 mmol/L will be considered missing.

9.3.2.2 Analysis Method

Absolute change in SwCl from baseline through Week 24 will be analyzed based on an MMRM that is the same as the primary efficacy endpoint. Data obtained from Day 15, Week 4, Week 8, Week 16, and Week 24 Visits will be included in the model, but the Day 15 Visit will not be included in the estimation of the average treatment effect through Week 24. The primary result obtained from the model will be the estimated treatment difference through Week 24 (defined as the average of Weeks 4, 8, 16, 24). The LS mean estimate with a 2-sided 95% CI and a 2-sided nominal *P* value will be provided. The treatment difference at each post-baseline visit, obtained from the model, will also be provided.

The LS mean (with SE) obtained from the MMRM analysis at each post-baseline visit up to Week 24 will be plotted by treatment group. In addition, the post-baseline raw values and the absolute change from baseline at each post-baseline visit up to Week 24 will be summarized descriptively (n, mean, SD, median, minimum, and maximum).

[redacted]

9.4 Safety Analysis

All safety analyses will be based on data from the TE period for all subjects in the Safety Set, unless otherwise specified. Subjects will be analyzed according to the treatment they actually received in the Treatment Period. For subjects receiving study drug from more than one treatment group, the treatment group allocation will be ELX/TEZ/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
- ECGs
- Vital signs
- Pulse oximetry

Only descriptive analysis of safety will be performed, and no statistical testing will be performed.

9.4.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs, or post-treatment AEs, defined as follows:

Pretreatment AE: any AE that occurred before the first dose date of study drug

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

Post-treatment AE: any AE that worsened (either in severity or seriousness) or that was newly developed after the 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 D.

An overview of all TEAEs by treatment group and overall will be summarized 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 Grade 3/4 TEAEs
- Subjects with related TEAEs
- Subjects with serious TEAEs
- Subjects with related serious TEAEs
- Subjects with TEAEs leading to death

The following summary tables of TEAEs 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
- Grade 3/4 TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Related TEAEs
- Serious TEAEs
- Related 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, TEAEs, and post-treatment AEs, will be presented in an individual subject data listing based on the All Subjects Set. In addition, listings containing individual subject adverse event data for TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, Grade 3/4 TEAEs, SAEs and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.

9.4.1.1 Adverse Events of Special Interest

For this study, elevated transaminase events and rash events, as determined by MedDRA preferred terms in Appendix F, are considered as adverse events of special interest.

For treatment-emergent elevated transaminase events and rash events, the following categories will be summarized by treatment group:

- 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 related serious events
- Subjects with events leading to death
- Duration of events
- Time-to-onset of first event

9.4.2 Clinical Laboratory

For the treatment-emergent laboratory measurements, the observed values and change from baseline values of the continuous hematology, serum chemistry, and coagulation results will be summarized in SI units by treatment group at each visit.

The number and percentage of subjects meeting at least 1 threshold analysis criterion, during the TE period, will be summarized by treatment group. The threshold analysis of shift from baseline will also be summarized for LFT laboratory parameters. The threshold analysis criteria are provided in Appendix E.

For selected LFT laboratory tests (alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALP], and total bilirubin), a scatter plot of the maximum treatment-emergent value versus the baseline value corresponding to ×ULN (upper limit of normal) will be presented by treatment group. Further, a scatter plot of the maximum treatment-emergent value of ALT and AST, separately, versus the maximum treatment-emergent value of total bilirubin corresponding to ×ULN will also be presented by treatment group.

Results of urinalysis and positive urine/serum pregnancy test will be listed in individual subject data listings only. For positive serum pregnancy listing, subjects with serum HCG which are abnormally high will be selected.

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

9.4.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided at each visit by treatment group for the following ECG interval measurements (in msec): RR interval, PR interval, QT interval, QTcF interval, QRS duration, and Heart Rate (beats per minute).

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

In addition, a listing containing individual subject ECG values will be provided. This listing will include data from both scheduled and unscheduled visits.

9.4.4 Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized at each visit by treatment group. The following vital signs parameters will be summarized: weight (kg), weight-for-age z-score, height (cm), height-for-age z-score, BMI (kg/m^2), BMI-for-age z-score, systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute).

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

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

9.4.5 Pulse Oximetry

For the treatment-emergent oxygen saturation values by pulse oximetry, a summary of observed values and change from baseline values will be provided at each visit by treatment group.

The number and percentage of subjects with shift from baseline category (classified as normal/missing and low according to the reference range) to the category at the lowest percent of oxygen saturation during the TE period will be summarized by treatment group. The reference range for normal oxygen saturation is specified as >95%, and <=95% for low oxygen saturation.

9.4.6 Ophthalmology Examination

Ophthalmology examination results will be provided in an individual subject data listing.

9.4.7 Physical Examination

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

9.4.8 COVID-19 Impacted Visits

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

10 Interim and DMC Analyses

10.1 Interim Analysis

No interim analysis is planned at this moment; otherwise, SAP will be amended.

10.2 DMC analysis

The DMC's objectives and operational details have been defined in a separate document (DMC Charter) which was finalized before the first subject was screened in the study. The DMC's planned safety reviews of study data is 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 (in study days)[2, 3, 4, 5]
Safety Assessment			
Serum Chemistry Hematology	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 16 Week 24 Safety Follow-up	1 15 29 57 113 169 Not applicable	≤1 Pre-dose [1, 22] (22, 43] (43, 85] (85, 141] (141, 183] Use nominal visit
Standard 12-lead ECG	Day 1 (Baseline) Week 8 Week 16 Week 24 Safety Follow-up	1 57 113 169 Not applicable	≤1 Pre-dose [1, 85] (85, 141] (141, 183] Use nominal visit
Vital signs (excluding BMI, Weight and Height, and their z-scores) and pulse oximetry	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 16 Week 24 Safety Follow-up	1 15 29 57 113 169 Not applicable	≤1 [1, 22] (22, 43] (43, 85] (85, 141] (141, 183] Use nominal visit
Coagulation	Day 1 (Baseline) Week 24	1 169	≤1 Pre-dose [1, 183]
BMI, Weight, Height and the corresponding z-scores	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 16 Week 24 Safety Follow-up	1 15 29 57 113 169 Not applicable	≤1 (1, 22] (22, 43] (43, 85] (85, 141] (141, 183] >183
Efficacy Assessment and Pharmacodynamic Assessment			
[redacted]			

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

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3, 4, 5]
Sweat Chloride Lung Clearance Index (LCI)	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 16 Week 24	1 15 29 57 113 169	≤1 Pre-dose (1, 22] (22, 43] (43, 85] (85, 141] (141, 183]

[redacted]

[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. If the latest measurement cannot be determined, then unscheduled visit will be selected

[3] For measurements collected on the date of first dose of study drug, 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 >183, then the ETT visit will be mapped into Safety Follow-up analysis visit.

[5] For efficacy assessments and nutrition variables (BMI, Weight, Height and their Z-scores), if there are multiple assessments >183, then nominal Safety Follow-up visit will be mapped to Safety Follow-up visit. If there is only ETT assessment > 183, the ETT visit will be mapped to the Safety Follow-up visit; else if there are multiple assessments with >183 then select the earliest record.

Derived Variables:

1. Age (in years) at first dose date and nominal visit (for demographics, listing and the calculation of [percent] predicted spirometry 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.

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

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

2. Age (in months) at nominal visit (for use in calculation of BMI, height 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.

4. Sweat Chloride:

   Non-missing sweat chloride concentrations from the left arm and right arm with assessment end date/time for a given arm up to 30 minutes after first dose time in treatment period will be considered for baseline.

5. Electrocardiogram:

   Baseline is defined as the most recent pretreatment measurement before the first dose of study drug in the Treatment Period. If multiple ECG measurements are obtained on the same calendar day during the TE period,

   - For summary purpose, the calculated average ECG will be used as the ECG value on that day;
   - For threshold analysis purpose, all reported ECG values will be used.

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 the inform consent date 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 the end of study date to impute).

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

Table 12-2 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 of TE period	-	-	A

P: Prior; C: Concomitant; A: Post

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

Appendix D: 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 TE 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 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 TE 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 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) if day is missing, or min (Dec, end of study participation) if month is missing.

Appendix E: Criteria for Threshold Analysis

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

Parameter	Threshold Analysis	Comments
Clinical Chemistry (LFT)		
ALT	>ULN - ≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >8x - ≤ 20xULN >20xULN	FDA DILI Guidance Jul 2009.
AST	>ULN - ≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >8x - ≤ 20xULN >20xULN	FDA DILI Guidance Jul 2009.
ALT or AST	(ALT>ULN - ≤ 3xULN) or (AST>ULN - ≤ 3xULN) (ALT>3x - ≤ 5xULN) or (AST>3x - ≤ 5xULN) (ALT>5x- ≤ 8xULN) or (AST>5x - ≤ 8xULN) (ALT>8x - ≤ 20xULN) or (AST>8x - ≤ 20xULN) ALT>20xULN or AST> 20xULN	FDA DILI Guidance
Alkaline Phosphatase	>ULN - ≤ 1.5xULN >1.5x - ≤ 2.5xULN >2.5x - ≤ 5xULN >5x - ≤ 20xULN >20xULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>ULN - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 3xULN >3x - ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
Direct Bilirubin	>ULN - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 3xULN >3x - ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
Indirect Bilirubin	>ULN - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 3xULN >3x - ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.

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

Parameter	Threshold Analysis	Comments
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	FDA DILI Guidance Jul 2009.
GGT	>ULN - ≤ 2.5xULN >2.5x - ≤ 5xULN >5x - ≤ 20xULN >20xULN	CTCAE grade 1-4
Clinical Chemistry (NON-LFT)		
Albumin	<LLN - ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>1x - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Creatinine	>ULN - ≤ 1.5xULN >1.5x - ≤ 3xULN >3x - ≤ 6xULN >6xULN	CTCAE grades 1-4
Lipase	>ULN - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
Creatine kinase	>ULN - ≤ 2.5xULN >2.5x - ≤ 5xULN >5x - ≤ 10xULN >10xULN	CTCAE grades 1-4
Hematology		
Hemoglobin	Hgb decreased (anemia) <LLN - ≥ 100 g/L <100 – ≥ 80 g/L < 80 g/L	CTCAE grade 1-3
	Hgb increased >ULN - ≤ 20 g/L above ULN >20 g/L above ULN - ≤ 40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3
Platelets	Platelet decreased <LLN - ≥ 75 x 10e9 /L <75 – ≥ 50 x 10e9 /L <50 – ≥ 25 x 10e9 /L <25 x 10e9 /L	CTCAE grade 1-4
	Platelet increased >ULN	No CTCAE available

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

Parameter	Threshold Analysis	Comments
Reticulocytes/Erythrocytes (%)	<LLN >ULN	No CTCAE
Coagulation		
Activated partial thromboplastin time (PTT)	>ULN - ≤ 1.5xULN >1.5x – ≤ 2.5xULN >2.5xULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤ 1.5xULN >1.5x – ≤ 2.5xULN >2.5xULN	CTCAE grade 1-3

Table 12-4 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
HR	Bradycardia ≤50 bpm	
	Tachycardia ≥140 bpm	
PR	≥200 ms and increase from baseline ≥20 ms	
QRS	≥120 ms	
QTc	Absolute values (ms) >450 ms (Male) or >470 ms (Female) ≥500 ms Increase from baseline Increase from baseline 30-60 ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula.

Table 12-5 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
Pulse Rate	Same as above in ECG category	
SBP	>120 mmHg < 70 mmHg	
DBP	>80 mmHg <50 mmHg	
Weight	Weight gain ≥5 % increase from baseline	CTCAE grade 1-3
	Weight loss ≥5 % decrease from baseline	CTCAE grade 1-3

Table 12-6 Threshold Analysis Criteria for Laboratory Tests

Parameter	Threshold Analysis	Comments
Clinical Chemistry (LFT)		
ALT or AST	>3xULN >5xULN >8xULN	

Appendix F: Adverse Events of Special Interest

Table 12-3 MedDRA Preferred Terms for Event of Special Interest

Adverse event of special interest	MedDRA preferred terms
Elevated transaminases	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 abnormal, Hepatic enzyme increased
Rash	Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash vesicular, Rash pruritic, Rash follicular, Rash pustular, Nodular rash, Drug eruption, Fixed eruption, Urticaria, Urticaria papular, Urticaria vesiculosa, Urticarial dermatitis, Rash morbilliform, Rash papular, Rash papulosquamous, Rash rubelliform, Rash scarlatiniform , Drug hypersensitivity, Type IV hypersensitivity reaction, Dermatitis, Dermatitis atopic, Epidermolysis, Skin toxicity, Dermatitis allergic, Dermatitis exfoliative, Dermatitis exfoliative generalised, Erythema multiforme, Exfoliative rash, Mucocutaneous rash, Acute generalised exanthematous pustulosis, Cutaneous vasculitis, Urticarial vasculitis, Dermatitis bullous, Drug reaction with eosinophilia and systemic symptoms, Epidermal necrosis, Oculomucocutaneous syndrome, Skin exfoliation, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, Perioral dermatitis, Vasculitic rash, Immune-mediated dermatitis, Penile rash, SJS-TEN overlap, Erythrodermic atopic dermatitis, Scrotal dermatitis, Anal Rash, generalised bullous fixed drug eruption

Note: the preferred terms listed in the table is based on the MedDRA version applicable at the time of finalization of the SAP. If the MedDRA version is upgraded at the time of the analysis, the corresponding preferred terms based on the upgraded version, including adding, removing and renaming the preferred terms, will be used in the analysis of adverse events of special interest.