VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX18-561-101 Version 2.0
(Final Analysis)

A Phase 2, Randomized, Double-blind Study to Evaluate the Efficacy and Safety of VX-561 in Subjects Aged 18 Years and Older With Cystic Fibrosis

Authors of SAP: [redacted]

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

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3 INTRODUCTION

This statistical analysis plan (SAP) for the final analysis is based on the approved clinical study protocol (CSP), Version 2.0, dated 03 Oct 2019, and most recent approved electronic case report form (eCRF), and approved eCRF completion guidelines.

This is a Phase 2, randomized, double-blind study to evaluate the efficacy and safety of VX-561 in subjects aged 18 years and older with cystic fibrosis.

The planned statistical analyses will contribute to evaluation of VX-561 doses based on totality of data, along with PK analysis and PK/PD analysis.

Per Protocol Version 2.0, the VX-561 25 mg qd and 50 mg qd treatment arms were discontinued ([redacted]). Most of the subjects randomized to the two dropped dose arms did not complete treatment. Therefore, the statistical analysis should be interpreted with caution.

This SAP (Methods) documents the planned statistical analyses of efficacy and safety endpoints for the final analysis.

The pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of VX-561 will also be evaluated in the study. Selected analyses related to sweat chloride will be documented in this SAP, other PK and PD analyses will be documented separately in the clinical pharmacology analysis plan (CPAP) and the Modeling and Simulation Plan for the study.

This SAP (Methods) will be finalized and approved prior to data lock and treatment unblinding for the final analysis.

The Vertex Biometrics Department will perform the statistical analysis within the scope of the SAP. SAS® Version 9.4 or higher software (SAS Institute, Cary, North Carolina, USA) will be used to generate all statistical outputs (tables, figures, listings, and datasets).

4 STUDY OBJECTIVES

4.1 Primary Objective

- To evaluate the efficacy of VX-561

4.2 Secondary Objectives

- To evaluate the PD effect of VX-561
- To evaluate the PK of VX-561, IVA, and relevant metabolites
- To evaluate the safety and tolerability of VX-561

5 STUDY ENDPOINTS

5.1 Primary Endpoint

- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline at Week 12

5.2 Secondary Endpoints

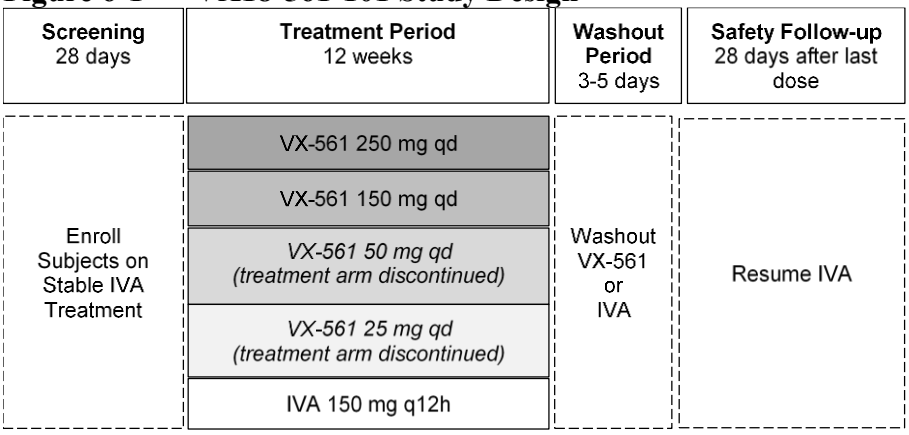
- Absolute change in sweat chloride concentrations from baseline at Week 12
- PK parameters of VX-561, IVA, and relevant metabolites
- Safety and tolerability, based on the assessment of adverse events (AEs), laboratory test results, standard 12-lead ECGs, vital signs, and pulse oximetry

6 STUDY DESIGN

6.1 Overall Design

This is a Phase 2 study of VX-561 monotherapy. A schematic of the study design is shown in Figure 6-1, which is randomized, double-blind, parallel-group, and active-controlled. The study was planned to evaluate 4 dose levels of VX-561 in subjects with CF who have a gating mutation and were previously taking a stable dose of IVA. Randomization will be stratified by ppFEV1 value at Screening (<70 versus ≥70). Per Protocol Version 2.0, the VX-561 25 mg qd and 50 mg qd treatment arms were discontinued ([redacted]); 44 subjects had been enrolled and randomized to the 5 treatment arms at that point. The remaining subjects planned to enroll will be randomized 2:2:1 to 3 treatment arms (VX-561 250 mg qd, VX-561 150 mg qd, and IVA 150 mg q12h).

Figure 6-1 VX18-561-101 Study Design



6.2 Sample Size and Power

The primary objective is to evaluate efficacy of VX-561. The primary efficacy endpoint is the absolute change in ppFEV1 from baseline at Week 12. Following discontinuation of the VX-561 25 mg qd and VX-561 50 mg qd treatment arms, the remaining subjects planned for enrollment will be randomized in a 2:2:1 ratio to the 3 current treatment arms. Assuming a within-group SD of 7 percentage points and a 10% dropout rate at Week 12: a sample size of 22 to 28 subjects in the VX-561 150, and 250 mg qd arms will provide a 95% CI of ± 3.4 to ± 2.9 percentage points around the observed mean absolute change in ppFEV1 from baseline at Week 12, based on 2 sided, 1-sample t statistics; a sample size of 11 to 14 subjects in the IVA 150 mg q12h arm will provide a 95% CI of ± 5.4 to ± 4.4 percentage points around the observed mean.

6.3 Randomization

An interactive web response system (IWRS) will be used to assign subjects to treatment. A randomization list will be produced by Vertex Biostatistics or a qualified randomization vendor.

Subjects will be assigned a unique subject number. Only subjects who have completed screening assessments and are eligible for participation in the study will be randomized to receive study drug during the Treatment Period. Randomization will be stratified by ppFEV1 (<70 versus ≥70) determined during screening.

6.4 Blinding and Unblinding

Please refer to Section 10.7 of the CSP for details.

7 ANALYSIS SETS

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

7.1 All Subjects Set

The **All Subjects Set** is defined as all subjects who were randomized or received at least 1 dose of study drug. The All Subjects Set will be used for 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* genotype and have received at least 1 dose of study drug in the Treatment Period. The FAS will be used for all PD and efficacy analyses in which subjects will be analyzed according to their randomized treatment group, unless otherwise specified.

7.3 Safety Set

The **Safety Set** will include all subjects who received at least 1 dose of study drug. The Safety Set will be used for all safety analyses and study drug exposure, unless otherwise specified. Subjects will be analyzed according to the treatment they received.

If a subject received doses from multiple treatment groups, the subject will be analyzed in the group with the highest priority, according to the order (from low priority to high priority) of IVA, VX-561 25 mg, VX-561 50 mg, VX-561 150 mg, VX-561 250 mg.

8 STATISTICAL ANALYSIS

8.1 General Considerations

The Schedule of Assessments is provided in Section 3 of the protocol. The precision standards for reporting safety and efficacy variables are provided in an internal Biometrics document that specifies the programming rules including the precision for derived variables.

All individual subject data for those randomized or dosed with any amount of study drug will be presented in data listings.

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. Percentages will be presented to 1 decimal place.

Treatment-emergent (TE) period will include the time period starting from the date of the first dose of study drug to 28 days after the date of the last study drug taken in the treatment period, or the completion date of study participation, whichever comes earlier. The TE Period will be used for safety analyses unless specified otherwise.

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. For ECG, baseline will be defined as the most recent non-missing pretreatment measurement (or the average of triplicate measurements, if the most recent non-missing pretreatment measurement is obtained in triplicate), before the first dose of study drug.

Absolute change from baseline will be calculated as postbaseline value – baseline value.

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

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

- In scheduled visit windows per specified visit windowing rules
- In the derivation of baseline and last on-treatment measurements
- In the derivation of maximum and minimum values during TE period, and maximum and minimum change from baseline values for safety analyses
- 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.

Multiplicity: There will be no multiplicity adjustment for performing multiple hypothesis tests, unless specified otherwise.

8.2 Background Characteristics

8.2.1 Subject Disposition

The number of subjects in the following categories will be summarized by treatment groups (IVA 150 mg q12h, VX-561 25 mg qd, VX-561 50 mg qd, VX-561 150 mg qd, VX-561 250 mg qd), VX-561 total (pooling all VX-561 arms) and overall (pooling all 5 arms):

- All Subjects Set
- Full Analysis Set
- Safety Set
- Randomized
- Randomized but not dosed in the Treatment Period

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

- Completed study drug treatment
- Prematurely discontinued treatment and the reason for discontinuation
- Completed study (i.e., completed Safety Follow-up Visit)
- Prematurely discontinued the study and the reason for discontinuation

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

8.2.2 Demographics and Baseline Characteristics

Demographics, medical history and baseline characteristics will be summarized based on the FAS, and presented by treatment groups, VX-561 total and overall.

Demographic data will include the following:

- Age at baseline (in years)
- Sex (female or 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)

Baseline characteristics will include the following:

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

Stratification categories will include the following:

- ppFEV1 at the Screening Visit (<70, ≥70)

Disease characteristics will include the following:

- $ppFEV_1$ at baseline (<40, ≥ 40 to <70, ≥70 to ≤100, >100)
- $ppFEV_1$ at baseline (continuous)
- Sweat Chloride at baseline (continuous)
- 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)
- Infection with *Pseudomonas aeruginosa* with 2 years prior to screening (Positive, Negative)

In addition, number (%) of subjects (based on the FAS) will be summarized by genotype category (*F508del/Gating*, *Gating/Gating* and *Gating/Other*) in a total column.

Data listings will also be provided for:

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

8.2.3 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 and preferred term. The corresponding data listing will also be provided.

8.2.4 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHODD, version March 2019, format B3 or the most updated version) and categorized as follows:

Prior medication: any medication that started before the date of 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, concomitant medication, or 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 considered in all 3 categories of prior, concomitant, and post-treatment medication.

Prior medications and concomitant medications will be summarized descriptively using frequency tables by Preferred Name based on the FAS, and presented by treatment groups, VX-561 total and overall.

All medications (including post-treatment medications) will be provided in an individual subject data listing. Details for imputing missing or partial start and/or stop dates of medication are described in Appendix B.

8.2.5 Study Drug Exposure

Study drug exposure (in days) will be calculated as: last dose date of study drug – first dose date of study drug + 1 day, regardless of study drug interruption. Exposure will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be

summarized in categories: ≤4 weeks, >4 to ≤8 weeks, >8 to ≤12 weeks, and >12 weeks, using counts and percentages.

Exposure summaries will be based on the Safety Set, and presented by treatment groups.

8.2.6 Study Drug Compliance

Study drug compliance will be calculated as: 100 x [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 drug on that day.

Percentage of study drug compliance will be summarized based on the FAS, and presented by treatment groups. Percentage of 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.

In addition, percentage of tablets taken will be calculated using the following formula: 100 x [(total number of tablets dispensed) – (total number of tablets returned)] / (total number of tablets planned to be taken per day x duration of study drug exposure in days). Summary similar to those for the study drug compliance will be produced based on the FAS. Due to discontinuation of the VX-561 25 mg qd and VX-561 50 mg qd treatment arms, the VX-561 25 mg tablet and its matching placebo were not dispensed following approval of Protocol v2.0; the calculations of drug compliance will not be conducted for the VX-561 25 mg tablet and its matching placebo.

8.2.7 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. A blinded protocol deviation review team will categorize IPDs according to the protocol deviation plan.

IPDs (from the clinical database or from the site deviation log) will be provided in an individual subject data listing.

8.3 Efficacy and Pharmacodynamic Analyses

All efficacy and PD analyses described in this section will be based on the FAS, unless otherwise specified.

8.3.1 Analysis of Primary Efficacy Variable

8.3.1.1 Definition of Variables

The primary efficacy variable is the absolute change in $ppFEV_1$ from baseline at Week 12. Percent predicted FEV_1 is the ratio of FEV_1 (L) and predicted FEV1 (L), expressed as a percentage. See Appendix C for more details

8.3.1.2 Primary Analysis

The primary efficacy endpoint is the absolute change in $ppFEV_1$ from baseline at Week 12. Per Protocol Version 2.0, the lower dose VX-561 arms (VX-561 25 mg qd and 50 mg qd) were discontinued. Most of the 17 subjects randomized to lower dose arms (VX-561 25 mg qd and 50

mg qd) did not complete study treatment. Due to the large proportion of missing assessments of lower dose arms, they are not included in MMRM analysis. The primary analysis (described below) is based on the within group mean of absolute change from baseline for VX-561 150 mg qd, VX-561 250 mg qd, and IVA 150 mg q12h treatment arms.

The primary analysis will be based on a mixed effects model for repeated measures (MMRM) using restricted maximum likelihood. The model will include the absolute change from baseline in $ppFEV_1$ at Day 15, Week 4, Week 8, and Week 12 from the current treatment arms (VX-561 150 mg qd, VX-561 250 mg qd, and IVA 150 mg q12h) as the dependent variable; treatment group, visit, and treatment by visit as fixed effects; with continuous baseline $ppFEV_1$ as covariates; and an unstructured covariance structure for the within-subject errors. If the model estimation does not converge, a compound symmetry covariance structure will be used. The efficacy data from the discontinued arms (VX-561 25 mg qd and VX-561 50 mg qd) will not be included in the model.

The primary results obtained from the model will be the within-group treatment effect estimate at Week 12 for each treatment arm. The adjusted mean with a 2-sided 95% CI will be presented in a table.

In addition, the adjusted mean and 95% CI of the treatment effect difference between each VX-561 arm and the IVA arm obtained from the MMRM model will be provided.

The $ppFEV_1$ values and absolute change from baseline values will be summarized descriptively (n, mean, SD, median, minimum and maximum) at each scheduled visit by treatment groups (in one table including IVA, VX-561 25 mg qd, VX-561 50 mg qd, VX-561 150 mg qd, VX-561 250 mg qd).

8.3.1.3 Sensitivity Analysis

No sensitivity analysis for the primary efficacy variable has been planned.

8.3.1.4 Subgroup Analysis

No subgroup analysis for the primary efficacy variable has been planned.

8.3.2 Analysis of Secondary Variable

8.3.2.1 Definition of Variables

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 $\geq$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.

8.3.2.2 Analysis of Pharmacodynamics Variable: Sweat Chloride

The secondary endpoint is the absolute change from baseline in sweat chloride at Week 12 and will be analyzed similarly to $ppFEV_1$, including VX-561 150 mg qd, VX-561 250 mg qd, and IVA 150 mg q12h treatment arms only. The model will include treatment group, visit, and treatment by visit as fixed effects; with continuous baseline $ppFEV_1$ as covariates. Adjusted

means and 95% CIs of the average treatment effects at Week 12 will be obtained for within-group (for each arm) and between-group comparisons (between each VX-561 arm and the IVA arm).

In addition, the sweat chloride raw values and change from baseline values will be summarized descriptively and similar to ppFEV1 analysis.

[redacted]

8.4 Safety Analysis

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

- AEs
- Clinical laboratory values (hematology, serum chemistry, coagulation, and urinalysis)
- Standard 12-lead ECGs

- Vital signs
- Pulse oximetry

Safety endpoints will be analyzed based on the Safety Set. Only a descriptive analysis of safety will be performed.

All safety data from the TE period will be summarized by treatment groups (including IVA, VX-561 25 mg qd, VX-561 50 mg qd, VX-561 150 mg qd, and VX-561 250 mg qd).

8.4.1 Adverse Events

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

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

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

Post-treatment AE: any AE that worsened or that was newly developed beyond the TE Period.

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

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

An overview of all TEAEs will be summarized in the following categories and presented by treatment groups and VX-561 total:

- Number of TEAEs (total number of TEAEs only)
- Subjects with any TEAEs
- Subjects with TEAEs by strongest relationship
- Subjects with TEAEs by maximum severity
- Subjects with TEAEs leading to treatment discontinuation (discontinuation of any study drug)
- Subjects with Grade 3/4 TEAEs
- Subjects with related TEAEs
- Subjects with TEAEs leading to treatment interruption (interruption of any study drug)
- Subjects with serious TEAEs
- Subjects with related serious TEAEs
- Subjects with TEAE leading to death

The following summary tables of TEAEs will be presented by treatment groups:

- All 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
- Grade 3/4 TEAEs

Summaries will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT) using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and 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 pre-treatment AEs, TEAEs, and post-treatment AEs, will be presented in an individual subject data listing based on the All Subjects Set.

8.4.2 Clinical Laboratory

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

The number and percentage of subjects with continuous hematology, chemistry and coagulation test values meeting at least 1 threshold analysis criterion event, during the TE period, will be summarized by treatment groups. The threshold analysis criteria are provided in Appendix E.

Results of urinalysis and positive urine/serum pregnancy tests 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.

8.4.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided at each scheduled visit by treatment groups, for the following ECG interval measurements (in msec): RR, PR, QT, and QT corrected for HR intervals (QTcF), QRS duration, and HR (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 groups. 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.

8.4.4 Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized by treatment groups. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), respiratory rate (breaths per minute), Weight (kg), and Body Mass Index (kg/m^2).

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE period will be summarized by treatment groups. 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.

8.4.5 Pulse Oximetry

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

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

In addition, a listing containing individual subject pulse oximetry values will be provided for each part. This listing will include data from both scheduled and unscheduled visits.

8.4.6 Physical Examination

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

[redacted]

[redacted]

9 INTERIM AND DMC ANALYSES

9.1 Interim Analysis

No interim analysis is planned.

9.2 DMC Analysis

The DMC's objectives and operational details are 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 are outlined in the DMC Charter and DMC Statistical Analysis Plan.

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10 REFERENCES

[1]Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall G, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.

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11 LIST OF APPENDICES

Appendix A: Analysis Visit Windows for Safety and Efficacy Assessments

Table 11-1 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days) [2,3,4]
Safety Analysis			
Serum Chemistry Hematology Weight/BMI	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 12 Safety Follow-up	1 15 29 57 85 Not applicable	≤1 Pre-dose [1, 22] Day 1 post dose (22, 43] (43, 71] (71, 99] Use nominal visit
Coagulation	Day 1 (Baseline; before dosing) Week 12 Safety Follow-up	1 Not applicable Not applicable	Use nominal visit for all post-baseline visits
Vital Signs Pulse Oximetry	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 12 Washout Visit Safety Follow-up	1 15 29 57 85 Not applicable Not applicable	≤1 Pre-dose [1, 22] Day 1 post dose (22, 43] (43, 71] (71, Week 12 visit date[5]] Use nominal visit Use nominal visit
Standard 12-Lead ECG	Day 1 (Baseline; before dosing) Week 4 Safety Follow-up	1 Not applicable Not applicable	Use nominal visit for all post-baseline visits
Efficacy and Pharmacodynamic Analysis			
Spirometry[6] Sweat Chloride[6]	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 12 Washout Visit Safety Follow-up	1 15 29 57 85 Not applicable Not applicable	≤1 Pre-dose (1, 22] (22, 43] (43, 71] (71, Week 12 visit date[5]] Use nominal visit Use nominal visit

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 the same visit window, use the following rules:
  - i. The measurement closest to the target day will be used; or
  - ii. If there are multiple measurements within the same distance from the target day, the latest measurement will be used.

3 For measurements collected on the date of first dose of study drug, if it cannot be determined whether the measurements are 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.

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Table 11-1 Analysis Visit Windows for Safety and Efficacy Assessments

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

4. When the ETT visit replaces the Safety Follow-up visit, it will be mapped to the Safety Follow-up visit. Other ETT visits will be mapped according to the analysis visit windowing rule for safety analysis.

5. If the week 12 visit is not available, then no assessment will be mapped to the Week 12 analysis visit.

6. Except for safety follow-up visit (or ETT replacing safety follow-up visit) and washout visit (given that Week 12 visit is completed), spirometry and sweat chloride assessments after last dose date will not be mapped to analysis visits.

Derived Variables

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

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

   Obtain informed consent date.

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

2. 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.

3. Sweat Chloride:

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

4. Electrocardiogram:

   Baseline is defined as the most recent pretreatment measurement before the first dose of study drug in the Treatment Period (or the average of triplicate measurements, if the most recent non-missing measurement is obtained in triplicate at screening). If multiple ECG measurements are obtained on the same visit during the TE period,

   - For summary purpose, the nominal scheduled ECG will be used as the ECG value for the visit;
   - For threshold analysis purpose, all reported ECG values will be used.

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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 informed 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 11-2 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

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Appendix C: Details of GLI Equations for Calculating ppFEV$_1$

Percent predicted values will be calculated for parameters of FEV_1, [redacted] using the Quanjer GLI-2012 Regression Equations and Lookup Tables.

The regression equations and lookup tables required to implement the Quanjer GLI-2012 predicted values are available in:

Quanjer GLI-2012 Regression Equations and Lookup Tables. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 7 April 2013. Available at:

http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/quanjer-gli-2012-regression-equations-and-lookup-tables.aspx.

[Accessed January 05, 2019].

The instructions and tools on how to implement the Quanjer GLI-2012 equations are:

Implementing GLI-2012 regression equations. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 19 July 2015. Available at:

http://www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools/it-engineers-and-manufacturers.aspx

[Accessed January 05, 2019].

GLI-2012 - SAS Macro. Sanja Stanojevic. Version 2, 7 April 2013. Available at:

http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/sas-macro.aspx

[Accessed January 5, 2019].

Data handling rule for spirometry is as follows:

- Input age with at least 2 decimal places.
- Use height at screening regardless if height is collected at study visit.
- For race, map CRF black or African American to black, all other races in CRF (except white) are mapped to 'other'; multiple checks for race in CRF are also mapped to 'other'; white is a reference race in the equations and assumes 0 values for all race coefficients in the GLI equations.

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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 study 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 with no imputation.
    - 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 the AE will be considered as TEAE for the Treatment Period.
    - else the AE will be considered as a pretreatment AE.

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) if day is missing, or min (Dec, end of study) if month is missing.

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Appendix E: Criteria for Threshold Analysis

Table 11-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Clinical Chemistry (LFT)		
ALT	>ULN - ≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >8x - ≤ 20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
AST	>ULN - ≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >8x - ≤ 20.0xULN >20.0xULN	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> 20 xULN	FDA DILI Guidance
Alkaline Phosphatase	>ULN - ≤ 1.5xULN >1.5 – ≤ 2.5 xULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>ULN - ≤ 1.5xULN >1.5 – ≤ 2xULN >2 – ≤ 3xULN >3 – ≤ 10xULN >10xULN	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.
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	FDA DILI Guidance Jul 2009.

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Table 11-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
GGT	>ULN - ≤ 2.5xULN >2.5 – ≤ 5.0xULN >5.0 – ≤ 20.0xULN >20.0xULN	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 >1.5 - ≤ 3.0xULN >3.0 - ≤ 6.0xULN >6.0xULN	CTCAE grades 1-4
Lipase	>ULN - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
CPK	>ULN - ≤ 2.5 x ULN >2.5 - ≤ 5 x ULN >5 - ≤ 10x ULN >10 x ULN	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 - ≥ 75.0 x 10e9 /L <75.0 – ≥ 50.0 x 10e9 /L <50.0 – ≥ 25.0 x 10e9 /L <25.0 x 10e9 /L	CTCAE grade 1-4
	Platelet increased >ULN	No CTCAE available

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Table 11-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

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

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Table 11-4 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
HR	Bradycardia	Per HV grade 2, 3, plus shift change
	<50 bpm	
	<45 bpm	
	Decrease from baseline ≥10 bpm	
	Decrease from baseline ≥20 bpm	
	<50 bpm and decrease from baseline ≥10 bpm	
	<50 bpm and decrease from baseline ≥20 bpm	
	Tachycardia	Per HV grade 1, 2, 3, plus shift change
	>100 bpm	
	>115 bpm	
	>130 bpm	
	Increase from baseline ≥10 bpm	
	Increase from baseline ≥20 bpm	
	>100 bpm and increase from baseline ≥10 bpm	
	>100 bpm and increase from baseline ≥20 bpm	
PR	≥240 ms	
	≥300 ms	
	≥200 ms and increase from baseline ≥40 ms	
	≥200 ms and increase from baseline ≥100 ms	
QRS	>110 ms	
	>160 ms	
	Increase from baseline ≥20 ms	
	Increase from baseline ≥40 ms	
QTc		To be applied to any kind of QT correction formula.
Borderline	>450 ms (Male) and <500ms; >470 ms and <500ms (Female)	
Prolonged	≥500 ms	
Additional	Increase from baseline	
	Increase from baseline >10 ms	
	Increase from baseline >20 ms	
	Increase from baseline >40 ms	
	Increase from baseline >60 ms	

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Table 11-5 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
HR	Same as above in ECG category	
SBP increased		809/770 analyses
	>140 mmHg	
	>160 mmHg	
	>10 mmHg increase from baseline	
	>20 mmHg increase from baseline	
	>140 mmHg and >10 mmHg increase from baseline	
	>140 mmHg and >20 mmHg increase from baseline	
	>160 mmHg and >10 mmHg increase from baseline	
	>160 mmHg and >20 mmHg increase from baseline	
SBP decrease		Per HV grade 1, 3, plus shift change
	<90 mmHg	
	<80 mmHg	
	>10 mmHg decrease from baseline	
	>20 mmHg decrease from baseline	
	<90 mmHg and >10 mmHg decrease from baseline	
	<90 mmHg and >20 mmHg decrease from baseline	
	<80 mmHg and >10 mmHg decrease from baseline	
	<80 mmHg and >20 mmHg decrease from baseline	

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Table 11-5 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
DBP increased		
	>90 mmHg	
	>100 mmHg	
	>5 mmHg increase from baseline	
	>10 mmHg increase from baseline	
	>90 mmHg and >5 mmHg increase from baseline	
	>90 mmHg and >10 mmHg increase from baseline	
	>100 mmHg and >5 mmHg increase from baseline	
	>100 mmHg and >10 mmHg increase from baseline	
DBP decreased		
	<60 mmHg	
	<45 mmHg	
	>5 mmHg decrease from baseline	
	>10 mmHg decrease from baseline	
	<60 mmHg and >5 mmHg decrease from baseline	
	<60 mmHg and >10 mmHg decrease from baseline	
	<45 mmHg and >5 mmHg decrease from baseline	
	<45 mmHg and >10 mmHg decrease from baseline	
Weight	Weight gain	CTCAE grade 1-3
	≥5 % increase from baseline	
	≥10 % increase from baseline	
	≥ 20% increase from baseline	
	Weight loss	CTCAE grade 1-3
	≥5 % decrease from baseline	
	≥10 % decrease from baseline	
	≥ 20% decrease from baseline	