VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX18-121-101 Version 4.0

A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-121 Combination Therapy in Subjects Aged 18 Years and Older With Cystic Fibrosis

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3 INTRODUCTION

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

This is a Phase 2, randomized, double-blind, placebo- and TEZ/IVA-controlled, parallel group, multicenter study to evaluate the safety and efficacy of VX-121 in triple combination with TEZ/VX-561 and in triple combination with TEZ/IVA in subjects aged 18 years and older with cystic fibrosis.

This SAP (Methods) documents the planned final statistical analyses of efficacy endpoints and safety endpoints defined in the study protocol for VX18-121-101.

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

The SAP (Methods) will be finalized and approved prior to the completion of Parts 1 and 2. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP prior to the completion of Parts 1 and 2. Any changes made to the SAP Methods after the completion of Parts 1 and 2 will be documented in the clinical study report for this study.

4 STUDY OBJECTIVES

4.1 Primary Objective

Parts 1 (Subjects with F/MF genotypes) and 2 (Optional; Subjects with the F/F genotype)

- To evaluate the safety and tolerability of VX-121 in TC with TEZ/VX-561 (deuterated IVA)
- To evaluate the efficacy of VX-121 in TC with TEZ/VX-561

[redacted]

4.2 Secondary Objectives

Parts 1 and 2

- To evaluate the pharmacodynamic (PD) effect of VX-121 in TC with TEZ/VX-561
- To evaluate the pharmacokinetics (PK) of VX-121 when administered in TC with TEZ/VX-561
- To evaluate the PK of TEZ, VX-561, and their respective metabolites when administered in TC with VX-121

[redacted]

5 STUDY ENDPOINTS

5.1 Primary Endpoint

- Safety and tolerability, based on the assessment of adverse events (AEs), laboratory test results, standard 12-lead ECGs, vital signs, and spirometry
- Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) through Day 29

5.2 Secondary Endpoints

- Absolute change from baseline in sweat chloride concentrations through Day 29
- Absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score at Day 29
- PK parameters of VX-121, TEZ, VX-561, [redacted] and relevant metabolites

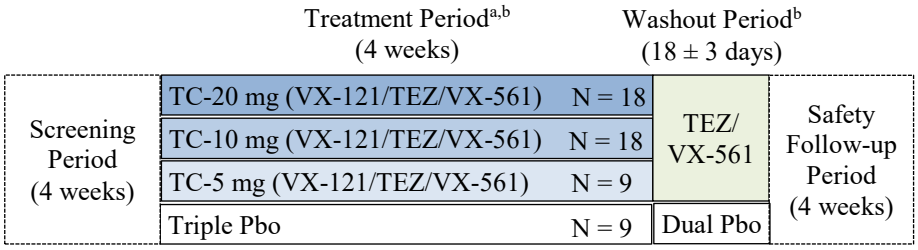
[redacted]

6 STUDY DESIGN

6.1 Overall Design

This is a Phase 2, [redacted] proof-of-concept study of VX-121. A schematic of the study design for Part 1 is shown in Figure 6-1, which has a randomized, double-blind, placebo-controlled, parallel-group design and evaluates VX-121 in TC with TEZ/VX-561.

Figure 6-1 VX18-121-101 Study Design for Part 1 (F/MF Genotypes)



F/MF: *F508del*/minimal function; N: number of subjects; Pbo: placebo; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; qd: daily; TC: triple combination; TEZ: tezacaftor

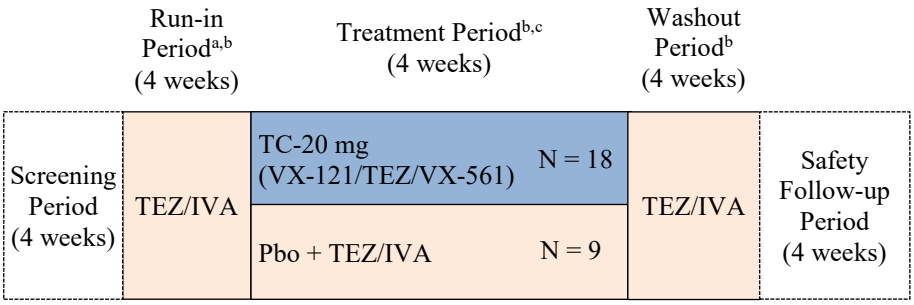
Note: Randomization will be stratified by ppFEV$_1$.

[a] The planned VX-121 doses are 5 mg, 10 mg, and 20 mg qd.

[b] The dosage of TEZ and VX-561 will be TEZ 100 mg qd and VX-561 150 mg qd.

A schematic of the study design for Part 2 is shown in Figure 6-2, which has a randomized, double-blind, TEZ/IVA-controlled, parallel-group design and evaluates VX-121 in TC with TEZ/VX-561.

Figure 6-2 VX18-121-101 Study Design for Part 2 (F/F Genotype)



FDC: fixed-dose combination; F/F: *F508del/F508del*; IVA: ivacaftor; N: number of subjects; Pbo: placebo; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; qd: daily; TC: triple combination; TEZ: tezacaftor

Note: Randomization will be stratified by ppFEV$_1$.

[a] All subjects are required to complete the TEZ/IVA Run-in Period to establish a reliable on-treatment (TEZ/IVA) baseline.

[b] The dosage of TEZ/IVA will be TEZ 100 mg qd/IVA 150 mg q12h, which will be administered as TEZ 100 mg/IVA 150 mg FDC in the morning and IVA 150 mg in the evening.

[c] Part 2 will evaluate the same VX-121 dose (20 mg qd) used in Part 1. The dosage of TEZ and VX-561 will be TEZ 100 mg qd and VX-561 150 mg qd.

6.2 Sample Size and Power

The primary objectives of Parts 1, 2, [redacted] are the evaluation of safety, tolerability, and efficacy of VX-121 in TC with TEZ/VX-561[redacted] in subjects with CF. The sample size calculations described below are deemed adequate to evaluate the primary objectives, based on clinical and statistical considerations.

Safety and Tolerability

The primary safety endpoints are safety and tolerability. Approximately 108 subjects with CF will be enrolled in the study with approximately 81 subjects receiving VX-121 in TC with either TEZ/VX-561 [redacted]. In case only Parts 1 and 2 are conducted, approximately 63 subjects will receive VX-121 in TC with TEZ/VX-561. The sample size for each treatment group will provide sufficient data for a descriptive analysis of AEs.

Efficacy

The primary efficacy endpoint is the absolute change from baseline in $ppFEV_1$ through Day 29. A sample size of 18 subjects per treatment group provides at least 90% power to detect a mean within-treatment change of 7 percentage points. These calculations assumed a standard deviation of 8 percentage points for the absolute change from baseline in $ppFEV_1$ and were based on EAST, Version 6.4.1.

6.3 Randomization

Only subjects who have completed screening assessments and are eligible for participation in the study (and completed the Run-in Period and qualify to enter the Treatment Period [Part 2]) will be randomized to receive active study drug or placebo or active control during the Treatment Period.

Randomization will be stratified by $ppFEV_1$ determined during screening (Day -28 to Day -1 assessment; <70 versus ≥70) in Parts 1 [redacted] and the TEZ/IVA Run-in Period (Day -14 assessment; <70 versus ≥70) in Part 2. If the Day -14 $ppFEV_1$ value is not valid or not available, the most recent available $ppFEV_1$ value before the date of randomization will be used for stratification.

An interactive web response system (IWRS) will be used to assign subjects to treatment.

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

7.3.1 Parts 1 [redacted]

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, unless otherwise specified. Subjects will be analyzed according to the treatment they received.

For subjects receiving study drug from more than one treatment group, the treatment group allocation will be the higher treatment group (in the increasing priority order: Triple placebo, TC-5 mg, TC-10mg, TC-20 mg).

7.3.2 Part 2

The **Safety Set for the Run-in Period** will include all subjects who received at least 1 dose of study drug TEZ/IVA in the Run-in Period. This Safety Set will be used for individual subject data listings for the Run-in Period, unless specified otherwise.

The **Safety Set for Treatment Period** will include all subjects who received at least 1 dose of study drug in the Treatment Period. This Safety Set will be used for all safety analyses for the Treatment Period, unless specified otherwise.

For subjects receiving study drug from more than one treatment group, the treatment group allocation will be the higher treatment group (VX-121/TEZ/VX-561 > TEZ/IVA).

8 STATISTICAL ANALYSIS

8.1 General Considerations

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

The analysis will be performed for each part, and presented separately for each part by treatment group, for the Treatment Period, unless specified otherwise. The treatment groups are defined as follows:

- Part 1:
    - Placebo
    - TC-5 mg (presented as “VX-121 5 mg qd/TEZ 100 mg qd/VX-561 150 mg qd” in tables, figures, listings (TFLs))
    - TC-10 mg (presented as “VX-121 10 mg qd/TEZ 100 mg qd/VX-561 150 mg qd” in TFLs)
    - TC-20 mg (presented as “VX-121 20 mg qd/TEZ 100 mg qd/VX-561 150 mg qd” in TFLs).

- Part 2:
    - Placebo + TEZ/IVA (presented as "Placebo/TEZ 100 mg qd/IVA 150 mg q12h" in TFLs)
    - TC-20 mg (presented as "VX-121 20 mg qd/TEZ 100 mg qd/VX-561 150 mg qd" in TFLs).

[redacted]

All individual subject data for those randomized or dosed with 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 for Parts 1 [redacted] will include the time from the first dose of study drug in the Treatment Period until 28 days after the last dose date of study drug (from treatment period or washout period) or the completion date of study participation (obtained from the end of follow-up page of the CRF), whichever occurs first.

For Part 2, the TE period will be defined separately for the Run-In Period, and the Treatment Period:

- The TE period for the Run-in Period will include the time from the first dose of study drug in the Run-in Period to: (1) the first dose of study drug in the Treatment Period for subjects who complete the Run-in Period and continue to the Treatment Period, or (2) 28 days after the last dose of study drug in the Run-in Period or the completion date of study participation (obtained from the end of follow-up page of the CRF), whichever occurs first, for subjects who do not continue to the Treatment Period.
- The TE period for the Treatment Period will include the time from the first dose of study drug in the Treatment Period to 28 days after the last dose of study drug (from treatment period or washout period) or the completion date of study participation (obtained from the end of follow-up page of the CRF), whichever occurs first.

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

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
- 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.

Spirometry ($ppFEV_1$) will be used for both efficacy and safety purposes. For efficacy analysis, the assessments will follow the visit windowing rules for efficacy. For safety analysis, the nominal visits will be used for $ppFEV_1$ collected at both pre-dose on Day 1 and pre-dose on Day 2 (for Part 1 only).

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.

Multiplicity: There will be no multiplicity adjustment for performing multiple hypothesis tests.

8.2 Background Characteristics

8.2.1 Subject Disposition

The number of subjects in the following categories will be presented by treatment group and overall for Parts 1 [redacted]:

- All Subjects Set;
- Randomized;
- Safety Set;
- Full Analysis Set;
- Randomized but not dosed.

The number of subjects for the Treatment Period in the following categories will be presented by treatment group and overall for Part 2:

- Randomized or dosed in the Treatment Period;
- Randomized;
- Safety Set for the Treatment Period;
- Full Analysis Set;
- 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 presented by treatment group and overall:

- Completed study drug treatment (Separated by Treatment Period and Washout Period for all parts);
- Prematurely discontinued treatment and the reason for discontinuation (i.e., discontinued all study drugs) (Separated by Treatment Period and Washout Period for all parts);
- Completed study (i.e., completed Safety Follow-up Visit);
- Prematurely discontinued the study and the reason for discontinuation.

A separate disposition table will be provided for the Run-in Period in Part 2 with the following categories:

- All Subjects Set
- Safety Set for the Run-in Period

The number and percentage (based on Safety Set for the Run-in Period) of subjects in each of the following disposition categories will be presented:

- Completed treatment in the Run-in Period;
- Prematurely discontinued treatment during run-in and the reason for treatment discontinuation;
- Prematurely discontinued study during run-in and the reason for study discontinuation.

A listing will be provided by part, for subjects who discontinued treatment (including the Run-in Period in Part 2) or who discontinued study with reasons for discontinuation.

8.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized based on the FAS, and presented by treatment group and overall, for each part.

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:

- $ppFEV_1$ at stratification (< 70 and ≥ 70)

  For Parts 1 [redacted] $ppFEV_1$ stratification (<70 versus ≥70) will be performed using the screening $ppFEV_1$ value.

  For Part 2, $ppFEV_1$ stratification (<70 versus ≥70) will be performed using the value obtained at Day -14 Visit

Disease characteristics will include the following:

- $ppFEV_1$ at baseline (<40, ≥ 40 to <70, ≥70 to ≤90, >90)
- $ppFEV_1$ at baseline (continuous)
- Sweat Chloride at baseline (continuous)
- FEV_1 (L) at baseline (continuous)
- CFQ-R respiratory domain score at baseline (continuous)
- Prior use of dornase alfa before first dose of study drug in the Treatment Period (Yes, No)
- Prior use of azithromycin before first dose of study drug in the Treatment Period (Yes, No)
- Prior use of inhaled antibiotic before first dose of study drug in the Treatment Period (Yes, No)
- Prior use of inhaled bronchodilator before first dose of study drug in the Treatment Period (Yes, No)
- Prior use of inhaled hypertonic saline before first dose of study drug in the Treatment Period (Yes, No)
- Prior use of inhaled corticosteroids before first dose of study drug in the Treatment Period (Yes, No)
- Infection with *Pseudomonas* aeruginosa within 2 years prior to screening (Positive, Negative)

In addition, 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.

In addition, the number of subjects reported to have had positive cultures for respiratory pathogens within the 2 years prior to screening (i.e., answered yes on the respiratory microbiology form) will be summarized for the FAS. The corresponding data listing will be provided.

8.2.4 Prior and Concomitant Medications

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

For Parts 1 [redacted]:

Prior medication: any medication that started before the first dose date 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 follows: prior, concomitant, post-treatment, both prior and concomitant, both concomitant and post-treatment, or prior, concomitant, and post-treatment.

For Part 2:

Prior medication: any medication started before the first dose of study drug in the Run-in Period.

Concomitant medication during the Run-in Period: medication continued or newly received during the TE period for the Run-in Period.

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

Post-treatment medication: medication continued or newly received after:

- the TE period for the Run-in Period for subjects who did not receive study drug in the Treatment period,

  or

- the TE period for the Treatment Period for the subjects who received study drug in the Treatment Period.

A given medication may be classified as any combination of the above categories, for example, prior and concomitant during the Run-in Period, concomitant during the Treatment Period and post-treatment, or concomitant during Run-in period, concomitant during Treatment Period, and post-treatment.

If a medication has completely missing or partially missing start/stop date and it cannot be determined whether it was taken before the first dose date of study drug, concomitantly, or after the TE period, it will be classified as prior, concomitant, and post-treatment.

For the FAS in Parts 1 [redacted] prior medications and concomitant medications will be summarized descriptively 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.

Prior and concomitant medication during the Run-in Period will be summarized together in one summary table for the FAS in Part 2 by treatment group. The concomitant medications during the treatment period will be summarized descriptively for Part 2 in the same way as for Part 1 [redacted] by treatment group for FAS.

Post-treatment medications will be listed for each subject. 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) for Treatment Period will be calculated as: last dose date of study drug – first dose date of study drug + 1 day, regardless of study drug interruption, and will be summarized descriptively for all parts.

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 in categories: ≤2 weeks, >2- ≤4 weeks, and >4 weeks for all parts, using counts and percentages.

Exposure summaries will be based on the Safety Set, and presented by treatment group and overall, for each part. For Part 2, exposure summaries will be based on the Safety Set for the Treatment Period.

8.2.6 Study Drug Compliance

Study drug compliance will be summarized for the Treatment Period only 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 during the Treatment Period) / (duration of study drug exposure in days during the Treatment Period)]. A study drug interruption on a given day is defined as an interruption of any study drugs on that day.

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 × [(total number of tablets dispensed for the Treatment Period) – (total number of tablets returned for the Treatment Period)] / (total number of tablets planned to be taken per day × duration of study drug exposure in days for the Treatment Period). Summary similar to those for the study drug compliance will be produced based on the FAS.

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. IPD rules will be developed and finalized before completion of Parts 1 and 2.

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 will be provided in an individual subject data listing for each part.

8.3 Efficacy Analysis

All efficacy analyses described in this section will be based on the FAS.

The analysis will include all available measurements through the last scheduled on-treatment visit including measurements after treatment discontinuation, per the visit windowing rules described in Appendix A.

8.3.1 Analysis of the Primary Efficacy Variable

8.3.1.1 Definition of Variable

The primary efficacy variable is the absolute change from baseline in percent predicted FEV_1 ($ppFEV_1$ in percentage units) through Day 29 in Parts 1, 2 [redacted].

The percent predicted FEV_1 is the ratio of FEV_1 (L) to the predicted FEV_1 (L), expressed as a percentage. The predicted FEV_1 will be calculated using the Global Lung Function Initiative[1] (GLI); details are in Appendix C.

8.3.1.2 Primary Analysis for Parts 1, 2 [redacted]

The null hypothesis to be tested is that the mean absolute within-group change from baseline in $ppFEV_1$ through Day 29 is zero for VX-121 in triple combination (TC) with TEZ/VX-561 in Parts 1 and 2, [redacted] separately. A 2-sided *p*-value of 0.05 or less will be interpreted as sufficient evidence to reject the null hypothesis.

The primary analysis will be performed using a mixed-effects model for repeated measures (MMRM) with change from baseline in $ppFEV_1$ at Day 15 and Day 29 as the dependent variable for each part, separately. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects and subject as a random effect, with the continuous baseline $ppFEV_1$ as a covariate. For Part 1 the model will include 4 treatment groups: placebo, TC-5 mg, TC-10 mg, TC-20 mg. For Part 2, the model will include 2 treatment groups: placebo + TEZ/IVA, and TC-20 mg. [redacted] 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. 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 $ppFEV_1$ data will be assumed to be missing at random; consequently, no imputation of missing data will be performed.

The adjusted means and 95% confidence intervals (CI) of the average treatment effect through Day 29 (average over Day 15 and Day 29 only) will be presented for all within-treatment and between-treatment comparisons, for each part. A 2-sided p-value will be provided for within-treatment comparisons.

Further, the adjusted mean and corresponding 95% CI for each treatment group and the treatment difference between each triple combination and placebo or TEZ/IVA at Day 15 and Day 29 will be provided, for each part. A 2-sided p-value will be provided for within-treatment comparisons.

The adjusted mean (with SE) obtained from the MMRM analysis at Day 15 and Day 29 will be plotted by treatment group, for each part.

In addition, for each part, a descriptive summary of observed values and the changes from baseline in $ppFEV_1$ will be presented for all treatment groups by post-baseline visit through the safety follow-up visit. A waterfall plot showing the subject-level absolute change in $ppFEV_1$ at Day 29 will be presented for each part.

[redacted]

8.3.1.4 Sensitivity Analysis

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

8.3.1.5 Subgroup Analysis

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

8.3.2 Analysis of Secondary Efficacy Variables

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 ≥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.

Cystic Fibrosis Questionnaire-Revised (CFQ-R):

The CFQ-R is a validated CF-specific instrument that measures quality-of-life domains. This study uses CFQ-R for Adolescents and Adult (subjects 14 years and older). CFQ-R for Adolescents and Adult has a total of 50 questions to form 12 domains. Question 43, which is scored 1, 2, 3, 4, or 5, is not used in calculating any domains; all the other 49 questions are scored 1, 2, 3, or 4.

To calculate the score for each domain, the response scores on the negatively phrased questions are reversed (reversed scores = 5 – response scores) so that 1 always represents the worst condition and 4 always represents the best condition. In each domain, in cases where individual questions were skipped, the missing scores are imputed with the mean score of the non-missing questions for that domain.

The scaled score for each domain ranges from 0 (worst condition) to 100 (best condition). It is calculated as follows:

Scaled score for a domain = 100 × (mean(scores of all questions in that domain) - 1)/3

The scaled score for a specific domain will not be calculated if more than half of the questions in the domain have missing scores.

Table 8-1 provides the questions included in each domain, the questions with the reversed scores, as well as the maximum number of missing questions allowed in order to be able to calculate a domain score.

Table 8-1 CFQ-R for Adolescents and Adults (subjects 14 years and older)

Domain	Questions		Questions with reversed scores	Maximum number of missing questions
	Total	Individual		
Physical	8	1, 2, 3, 4, 5, 13, 19, 20	13	4
Role	4	35, 36, 37, 38	35	2
Vitality	4	6, 9, 10, 11	6, 10	2
Emotion	5	7, 8, 12, 31, 33	-	2
Social	6	22, 23, 27, 28, 29, 30	23, 28, 30	3
Body	3	24, 25, 26	-	1
Eat	3	14, 21, 50	-	1
Treatment burden	3	15, 16, 17	15, 17	1
Health perceptions	3	18, 32, 34	18, 32, 34	1
Weight	1	39	-	0
Respiration*	6	40, 41, 42, 44, 45, 46	43	3
Digestion	3	47, 48, 49	-	1

*: Question 43 not used to calculate any domain.

8.3.2.2 Analysis Method

8.3.2.2.1 Absolute Change from baseline in Sweat Chloride through Day 29 (Parts 1, 2[redacted])

The analysis of the absolute change from baseline in sweat chloride through Day 29 will be based on an MMRM similar to the primary analysis of the primary efficacy variable for Parts 1, 2, [redacted]. The presentation of results will also be similar.

8.3.2.2.2 Absolute change from baseline in the CFQ-R respiratory domain score at Day 29 (Parts 1, 2 [redacted])

The absolute change from baseline in the CFQ-R respiratory domain score at Day 29 will be based on the *CFQ-R scaled scores*.

An MMRM similar to the primary analysis of the primary efficacy variable in Parts 1, 2 [redacted] will be used to analyze this variable. The presentation of results will also be similar.

[redacted]

[redacted]

8.4 Safety Analysis

For Parts 1 [redacted] all safety analyses will be based on data from the TE Period for all subjects in the Safety Set. For Part 2, all safety analyses will be based on the TE Period for the Treatment Period for all subjects in the corresponding Safety Set for Treatment Period, unless otherwise specified.

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

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., hematology, serum chemistry, coagulation, and urinalysis)
- ECGs
- Vital signs including body weight and BMI
- Pulse oximetry
- Spirometry.

All safety data will be summarized by treatment group unless otherwise specified, for each part. Only descriptive analysis of safety will be performed and no statistical testing will be performed. The safety data during the Run-in Period will only be presented in listings, unless otherwise specified.

8.4.1 Adverse Events

For Parts 1 [redacted]

For analysis purposes, AEs will be classified as pretreatment AEs, 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 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 Part 2:

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs during the Run-in Period, TEAEs during the Treatment Period, and post-treatment AEs, defined as follows:

Pretreatment AE: any AE that started before the first dose date of study drug (TEZ/IVA) in the Run-in Period.

TEAE during the Run-in 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 (TEZ/IVA) through the end of the TE period for the Run-in Period.

TEAE during the Treatment 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 (TC or placebo+TEZ/IVA) through the end of the TE period for the Treatment Period.

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

- the TE period for Run-in Period if the subject did not receive treatment in the Treatment Period, or
- the TE period for the Treatment Period if the subject received treatment in the Treatment 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 for Parts 1 [redacted] or if there is no clear evidence that the AEs are pre-treatment or TEAE during the Run-in Period or post-treatment for Part 2, the AEs will be classified as TEAEs during the Treatment Period. Unless otherwise specified, TEAE refers to TEAE during the Treatment Period.

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

AE summary tables will be presented for TEAEs only, for the TE period for Parts 1 [redacted] and the TE period for Treatment Period in Part 2.
An overview of all TEAEs by treatment group and overall will be summarized in the following categories:

- 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 study drug discontinuation (discontinuation of any study drug);
- Subjects with TEAEs leading to study drug interruption (interruption of any study drug);
- Subjects with Grade 3/4 TEAEs;
- Subjects with related TEAEs;
- 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 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

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.

Additional summary tables will be presented by treatment group and by PT for TEAEs showing number and percentage of subjects.

All AEs, including pre-treatment AEs, TEAEs for all applicable periods, and post-treatment AEs, 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, Grade 3/4 TEAEs, SAEs and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.

In addition, the following tables for the Run-in period will be presented by overall based on the Safety Set for the Run-in period.

- An overview of TEAEs during the Run-in Period
- All TEAEs during the Run-in Period by SOC and PT

8.4.2 Clinical Laboratory

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

The number and percentage of subjects meeting at least 1 threshold analysis criterion event, during the TE period for Parts 1 [redacted] or the TE period for Treatment Period for Part 2, will be summarized by treatment group for each part. The threshold analysis criterion shift from baseline will also be summarized for selected laboratory parameters. The threshold analysis criteria are provided in Appendix E.

For selected LFT laboratory test (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin), a scatter plot of the maximum treatment-emergent value versus the baseline value corresponding to ×ULN will be presented. 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, for each part.

Results of abnormal urinalysis and positive urine/serum pregnancy test will be listed in individual subject data listings only.

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 changes from baseline values will be provided at each scheduled visit and time point, by treatment group, for each part, for the following ECG interval measurements (in msec): RR interval, PR interval, QT interval, and QT corrected for HR (QTcF) interval, QRS duration, and Heart Rate (HR) (beats per minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE period for Parts 1 [redacted] or the TE period for the Treatment Period in Part 2, will be summarized by treatment group, for each part. 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 changes from baseline values will be summarized by treatment group, at each scheduled visit, for each part. 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 BMI (kg/m^2).

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE period for Parts 1 [redacted] or the TE period for the Treatment Period for Part 2 will be summarized by treatment group, for each part. 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 changes from baseline values will be provided at each scheduled visit, for the percent of oxygen saturation, by treatment group, for each part.

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 for Parts 1 [redacted] or the TE period for the Treatment Period for Part 2 will be summarized by treatment group, for each part.

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.

8.4.7 Change from Day 1 to Day 2 in Pre-dose Spirometry (Part 1 only)

A summary of the pre-dose values for $ppFEV_1$ on Days 1 and 2 and change from Day 1 predose value for the $ppFEV_1$ value on Day 2 will be presented on nominal visits Day 1 and Day 2 by treatment group for the subjects in Safety Set who had non-missing Day 1 pre-dose and Day 2 pre-dose spirometry assessments in Part 1. Further, a box plot of differences (Day 2 – Day 1 pre-dose) will be presented by treatment group.

[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.

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.

11 LIST OF APPENDICES

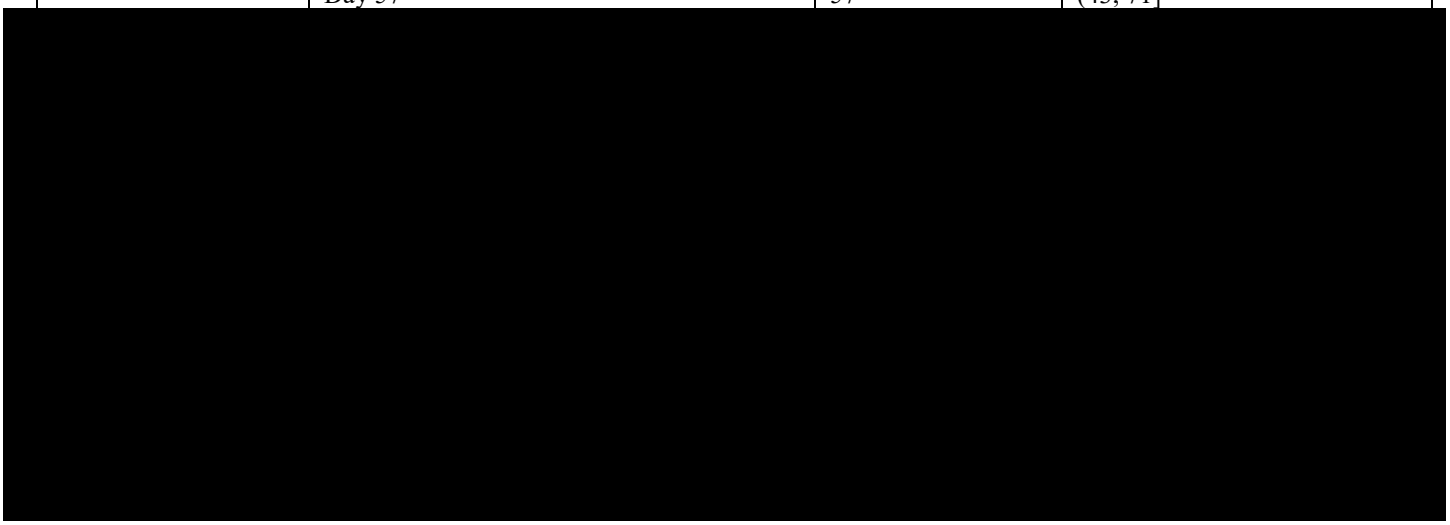
Appendix A: Analysis Visit Windows for Safety and Efficacy Assessments

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]
Part 1			
Serum Chemistry Hematology Coagulation Weight Standard 12-lead ECG	Day 1 (Baseline) Day 8 Day 15 Day 29 Safety Follow-up	1 8 15 29 Not applicable	≤1 Pre-dose [1, 12] Day 1 post dose (12, 22] (22, 52] Use nominal visit
Vital Signs Pulse Oximetry	Day 1 (Baseline) Day 2 (Subjects with Day 2 SP consent) Day 8 (Subjects with Day 2 SP consent) Day 8 (Subjects without Day 2 SP consent) Day 15 Day 29 Day 47 Safety Follow-up	1 2 8 8 15 29 47 Not applicable	≤1 Pre-dose [1, 2] Day 1 post dose (2, 12] [1, 12] Day 1 post dose (12, 22] (22, 38] (38, 61] Use nominal visit
Spirometry (Safety analysis of change from Day 1 to Day 2 in pre-dose ppFEV$_1$)	Day 1 Day 2	1 2	Use nominal visit Use nominal visit
Spirometry	Day 1 (Baseline) Day 8 (Subjects with Day 2 SP consent) Day 8 (Subjects without Day 2 SP consent) Day 15 Day 29 Day 47 Safety Follow-up	1 8 8 15 29 47 Not applicable	≤1 Pre-dose [2, 12] Day 2 post dose [1, 12] Day 1 post dose (12, 22] (22, 38] (38, 61] Use nominal visit
Sweat Chloride	Day 1 (Baseline) Day 15 Day 29 Day 47 Safety Follow-up	1 15 29 47 Not applicable	≤1 Pre-dose [1, 22] Day 1 post dose (22, 38] (38, 61] Use nominal visit
CFQ-R	Day 1 (Baseline) Day 15 Day 29	1 15 29	≤1 Pre-dose [1, 22] Day 1 post dose (22, 61]
[redacted]			
Part 2			

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]
Serum Chemistry Hematology Vital Signs Weight Pulse Oximetry Standard 12-lead ECG	Day 1 (Baseline) Day 8 Day 15 Day 29 Day 43 Day 57 Safety Follow-up	1 8 15 29 43 57 Not applicable	≤1 Pre-dose [1, 12] Day 1 post dose (12, 22] (22, 36] (36, 50] (50, 71] Use nominal visit
Coagulation	Day 1 (Baseline) Day 8 Day 15 Day 29 Safety Follow-up	1 8 15 29 Not applicable	≤1 Pre-dose [1, 12] Day 1 post dose (12,22] (22, 57] Use nominal visit
Spirometry	Day 1 (Baseline) Day 8 Day 15 Day 29 Day 43 Day 57 Safety Follow-up	1 8 15 29 43 57 Not applicable	≤1 Pre-dose [1, 12] Day 1 post dose (12, 22] (22, 36] (36, 50] (50, 71] Use nominal visit
Sweat Chloride	Day 1 (Baseline) Day 15 Day 29 Day 43 Day 57	1 15 29 43 57	≤1 Pre-dose [1, 22] Day 1 post dose (22, 36] (36, 50] (50, 71]
CFQ-R	Day 1 (Baseline) Day 15 Day 29 Day 57	1 15 29 57	≤1 Pre-dose [1, 22] Day 1 post dose (22, 43] (43, 71]



[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 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. If there is a scheduled and unscheduled assessment on the same date (no time collected), the unscheduled one should be considered as the latest measurement.
[3] For lab, ECG and vital sign measurement collected on the date of first dose of study drug in Treatment Period, 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.

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 for the Treatment Period

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

3. Missing last dose date for Treatment Period

   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

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]

drug administration date from EX SDTM domain, as appropriate, The imputation algorithm will ensure the imputed last dose date does not exceed Day 29 visit date.

4. 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.

5. 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). 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 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 in Parts 1 [redacted]

	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

Table 11-3 Prior, Concomitant, and Post Categorization of a Medication in Part 2

	Medication Stop Date			
Medication Start Date	**< First Dose Date of Run-in TE Period**	**≥ First Dose Date and ≤ End Date of Run-in TE Period**	**≥ First Dose Date and ≤ End Date of Treatment TE Period**	**> End Date of Treatment TE Period**
< First dose date of Run-in TE period	P	PC1	PC1C2	PC1C2A
≥ First dose date and ≤ End date of Run-in TE Period	-	C1	C1C2	C1C2A
≥ First dose date and ≤ End date of Treatment TE Period	-	-	C2	C2A
> End date of Treatment TE Period	-	-	-	A

P: Prior; C1: Concomitant during the Run-in Period; C2: Concomitant during the Treatment Period; A: Post

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 and height with at least 2 decimal places.
- Use height at screening.
- For race, map the 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.

Appendix D: Imputation Rules for Missing AE dates

D.1 Parts 1 [redacted]

Imputation rules for missing or partial AE start date for Parts 1 [redacted] 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 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 the 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.

D.2 Part 2

Imputation rules for missing or partial AE start date for Part 2 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 if AE start year and month are equal to the month and year of first dose date of the Run-in Period, then impute the AE start day as the day of first dose date of the Run-in Period;
        - else impute the AE start day as 1.
    - else if the full (or partial) AE end date is NOT before the first dose date of the Run-in Period, then;
        - if AE start year and month are equal to the month and year of first dose date of the Run-in Period, then impute the AE start day as the day of first dose date of the Run-in 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 during the Run-in Period, TEAE during the Treatment 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 if AE start year is equal to the year of first dose date of the Run-in Period, then impute the AE start month and day as the month and day of first dose date of the Run-in Period;
        - else impute the AE start month as January and day as 1.
    - else if the full (or partial) AE end date is NOT before the first dose date of the Run-in Period, then;
        - if AE start year is equal to the year of first dose date of the Run-in Period, then impute the AE start month and day as the month and day of first dose date of the Run-in 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 during the Run-in Period, TEAE during the Treatment 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 if the full (or partial) AE end date is NOT before the first dose date of the Run-in Period, then impute the AE start date as the date of first dose date of the Run-in Period.
  - else impute AE date as 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) if day is missing, or min (the last day of Dec, end of study) if month is missing.

Appendix E: Criteria for Threshold Analysis

Table 11-4 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.
Indirect Bilirubin	>ULN - ≤ 1.5xULN >1.5 – ≤ 2xULN >2 – ≤ 3xULN >3 – ≤ 10xULN >10xULN	
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.

Table 11-4 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
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.
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	>ULN - ≤ 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
Creatine kinase	>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

Table 11-4 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
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
Reticulocytes/Erythrocytes (%)	<LLN >ULN	No CTCAE
Coagulation		
Activated Partial thromboplastin time (PTT)	>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

Table 11-5 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	>450 and <500ms (Male); >470 and <500ms (Female)	To be applied to any kind of QT correction formula.
	≥500 ms	
	Increase from baseline	
	Increase from baseline >10 ms	
	Increase from baseline >20 ms	
	Increase from baseline >40 ms	
	Increase from baseline >60 ms	

Table 11-6 Threshold Analysis Criteria for Vital Signs

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

Table 11-6 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 ≥5 % increase from baseline ≥10 % increase from baseline ≥ 20% increase from baseline	CTCAE grade 1-3
	Weight loss ≥5 % decrease from baseline ≥10 % decrease from baseline ≥ 20% decrease from baseline	CTCAE grade 1-3