VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX18-659-106, Version 1.0

A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-659/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age

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2 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
bpm	beats per minute
CF	cystic fibrosis
[redacted]	[redacted]
CFTR	cystic fibrosis transmembrane conductance regulator protein or the gene encoding the protein.
CI	confidence interval
CRF	case report form
CRO	contract research organization
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDC	fixed-dose combination
[redacted]	[redacted]
FEV_1	forced expiratory volume in 1 second
[redacted]	[redacted]
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F/F	homozygous for *F508del*
F/MF	heterozygous for *F508del* and a *CFTR* minimal function mutation
IVA	ivacaftor
LS means	Least squares means
LFT	liver function test
max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function
min	minimum value
MMRM	mixed model repeated measure
N	number of subjects
PD	pharmacodynamic/pharmacodynamics
PK	pharmacokinetic/pharmacokinetics
$ppFEV_1$	percent predicted FEV_1
PT	preferred term
q12h	every 12 hours
QRS	Q, R, and S-wave define the QRS-complex in an ECG
QT	QT interval: The duration of ventricular depolarization and subsequent repolarization; it is measured from the beginning of the QRS complex to the end of the T wave

Abbreviation	Term
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate with Fridericia's correction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SOC	system organ class
TC	triple combination
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
ULN	upper limit of normal
WHODD	World Health Organization Drug Dictionary Enhanced

4 INTRODUCTION

Study VX18-659-106 (Study 659-106) is a Phase 3, [redacted] multicenter study evaluating the pharmacokinetics (PK), safety, and tolerability of VX-659 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects 6 through 11 years of age (inclusive) with cystic fibrosis (CF) who are either homozygous for *F508del* mutation (F/F) or heterozygous for *F508del* and a minimal function mutation (F/MF).

This statistical analysis plan (SAP) for Study 659-106 is based on the most recent approved clinical study protocol (CSP), the most recent approved electronic case report form (eCRF), and the most recent approved eCRF completion guidelines.

This SAP (Methods) documents the planned statistical analyses of safety and efficacy endpoints for the study. It also documents analyses for additional safety and efficacy variables not specified in the protocol.

[redacted] PK and PD (if applicable) analyses will be documented separately in the clinical pharmacology analysis plan (CPAP) for the study.

The Vertex Biometrics Department or designee will perform the statistical analysis of the safety and efficacy data; SAS (Version 9.4 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the data lock for Part A. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP.

5 STUDY OBJECTIVES

5.1 Primary Objectives

Part A

To evaluate the PK of VX-659, TEZ, and IVA when dosed in TC [redacted]

5.2 Secondary Objectives

Part A

- To evaluate the PK of TEZ and IVA metabolites
- To evaluate the safety and tolerability of VX-659/TEZ/IVA [redacted]

6 STUDY ENDPOINTS

6.1 Primary Endpoint

Part A

PK parameters of VX-659, TEZ, and IVA, including C_{max}, C_{trough}, and $AUC_{0-\tau}$

[redacted]

6.2 Secondary Endpoints

Part A

- PK parameters of TEZ and IVA metabolites, including C_{max}, C_{trough}, and $AUC_{0-\tau}$
- Safety and tolerability as determined by AEs, clinical laboratory values, standard 12-lead ECGs, vital signs and pulse oximetry

[redacted]

7 STUDY DESIGN

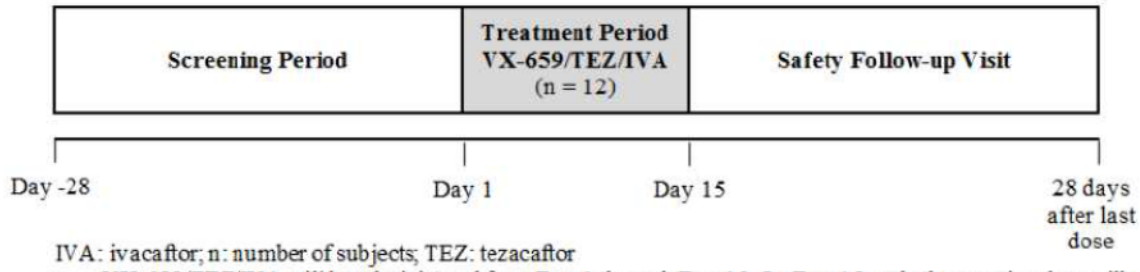
7.1 Overall Design

This is a Phase 3, [redacted], multicenter study evaluating the PK, safety, and tolerability of VX-659/TEZ/IVA TC therapy in CF (F/F and F/MF genotypes) subjects 6 through 11 years of age (inclusive).

Part A

A schematic of the study design for Part A is provided in Figure 7-1. Approximately 12 subjects (F/F or F/MF genotypes) are planned for enrollment. During the Treatment Period, subjects will be administered VX-659/TEZ/IVA for approximately 15 days. A review of safety, tolerability, and available PK data will be completed by an internal Vertex team after Part A [redacted]. Additional subjects may be enrolled as needed in Part A, based on emerging PK data, [redacted]

Figure 7-1 Part A Study Design



IVA: ivacaftor; n: number of subjects; TEZ: tezacaftor
[a] VX-659/TEZ/IVA will be administered from Day 1 through Day 15. On Day 15, only the morning dose will be administered.

[redacted]

[redacted]

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

Table 7-1 Part A [redacted] Doses

Subjects Weight	VX-659 Dose	TEZ Dose	IVA Dose
Part A			
All subjects	120 mg qd	50 mg qd	75 mg q12h
[redacted]			

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

[redacted]

7.2 Sample Size and Power

Part A

Approximately 12 subjects will be enrolled in Part A. Sample size calculations were determined based on VX-659 PK, using noncompartmental analysis (NCA)-based parameters, such as clearance and volume of distribution. Based on the variability observed in adults, data from 12 subjects will allow 80% power to target a 95% CI within 60% and 140% of the geometric mean estimate of clearance for VX-659.

[redacted]

[redacted]

7.3 Randomization

Part A [redacted]

Randomization is not required.

7.4 Blinding and Unblinding

Part A [redacted]

Refer to Section 10.7 of the CSP for details.

8 ANALYSIS SETS

Part A [redacted]

The analysis set will be defined separately for Part A [redacted]

8.1 All Subjects Set

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

8.2 Safety Set

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

8.3 Full Analysis Set

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

9 STATISTICAL ANALYSIS

9.1 General Considerations

Part A [redacted]

Data from Part A [redacted] will be analyzed separately.

The Schedule of Assessments is provided in Section 3 of the CSP. 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.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (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.

Baseline unless otherwise specified, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in the corresponding Part.

[redacted]

Absolute change from baseline will be calculated as Post-baseline value − Baseline value.

Relative change from baseline will be calculated and expressed in percentage as 100% × (Post-baseline value − Baseline value) / Baseline value.

Treatment-emergent (TE) Period for Part A [redacted] will include the time from the first dose of study drug in the corresponding Part through 28 days after the last dose or the completion of study participation date in the corresponding Part, whichever occurs first.

Refer to Section 9.1.6 of the CSP for the definition of completion of study participation.

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 during TE period 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.

9.2 Background Characteristics

9.2.1 Subject Disposition

Part A [redacted]

The number of subjects in the following categories will be summarized based on the All Subjects Set:

- All Subjects Set
- Safety Set
- FAS

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

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

[redacted]

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

9.2.2 Demographics and Baseline Characteristics

Part A [redacted]

Demographics and baseline characteristics will be summarized based on the FAS.

Demographic data will include the following:

- Age at baseline (in years)
- Sex (male, female)
- 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)
- Geographic region

Baseline characteristics will include the following:

- CFTR genotype group (F/F, F/MF)
- Weight group (<25 kg, ≥25 kg to <40 kg, and ≥40 kg)
- Weight (kg)

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

[redacted]

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

9.2.3 Medical History

Part A [redacted]

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

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.

9.2.4 Prior and Concomitant Medications

Part A [redacted]

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

- **Prior medication:** any medication that administered during the 56 days before the first dose of study drug in the corresponding Part.
- **Concomitant medication:** medication continued or newly received during the corresponding TE Period.
- **Post-treatment medication:** medication continued or newly received after the corresponding 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.

If a medication has a completely missing or partially missing start date or stop date and it cannot be determined whether it was taken before the first dose date, concomitantly, or after the TE period, it will be classified as prior, concomitant, and post-treatment. Details for imputing missing or partial start and/or stop dates of medication are described in Appendix B.

Concomitant medications will be summarized descriptively for the FAS using frequency tables by: 1) preferred name (PN); and 2) anatomic class (ATC) level 1, ATC level 2, and PN. [redacted] All medications will be listed for each subject.

9.2.5 Study Drug Exposure

Part A [redacted]

Study drug exposure summaries will be based on the Safety Set.

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

Study drug exposure (in days for Part A; [redacted]) will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized using counts and percentages for Treatment Period categories. For Part A, categories are specified as: ≤2 days; >2 and ≤4 days; >4 and ≤8 days; >8 and ≤15 days; >15 days. [redacted] Additionally, the total study drug exposure, defined as the sum total of the study drug exposure across all subjects (in patient-weeks for Part A; in patient-weeks [redacted]), will be provided.

9.2.6 Study Drug Compliance

Part A [redacted]

Study drug compliance will be summarized based on the FAS.

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

defined as an interruption of any study drug dose or component on that day. [redacted]

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) − (total number of tablets returned)] / (total number of tablets planned to be taken per day × duration of study drug exposure in days). A summary similar to that for study drug compliance will be produced based on the FAS.

9.2.7 Important Protocol Deviations

Part A [redacted]

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 the data lock for Part A.

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

- Subject was enrolled in the study despite not satisfying one or more inclusion/exclusion criterion
- 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

The occurrence of any of these events should be considered as a potential IPD, but the team should categorize such an event as an IPD only if it has the potential to affect the completeness, accuracy, or reliability of the study data or the subject's rights, safety, or well-being.

For Part A, IPDs will only be provided in an individual subject data listing. [redacted]

[redacted]

[redacted]

9.4 Safety Analysis

Part A [redacted]

Safety is a secondary objective of Part A, [redacted]. All safety analyses will be conducted for Part A [redacted], based on data from the corresponding TE Period in the Safety Set.

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
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry

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

9.4.1 Adverse Events

Part A [redacted]

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

- **Pretreatment AE:** any AE that occurred before the first dose date of study drug in the corresponding Part.
- **TEAE:** any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose of study drug through the end of the TE period in the corresponding Part.
- **Post-treatment AE:** any AE that worsened (either in severity or seriousness) or that was newly developed after the TE period in the corresponding Part.

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

Details for imputing missing or partial start dates of adverse events are defined in Appendix E.

An overview of all TEAEs will be provided with 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 TEAEs leading to death

The following summary tables of TEAEs will be presented:

- All TEAEs
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Serious TEAEs
- TEAEs leading to death
- Grade 3/4 TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- Related TEAEs
- [redacted]

Summaries will be presented by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects, subjects with multiple occurrences of the same AE or a continuing AE will be counted once and only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries.

Additional summary tables will be provided for TEAEs showing number and percentage of subjects

- All TEAEs by PT

All AEs, including pretreatment AEs, TEAEs, and post-treatment AEs, will be presented in an individual subject data listing based on the All Subjects Set. In addition, a listing 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.

For all AEs, the eCRF captures the action taken for VX-659/TEZ/IVA pills separately from the action taken for IVA monotherapy pills. As a result, it is possible that, in the final database for Part A [redacted], the AE actions taken for the two agents (fixed dose VX-659/TEZ/IVA and ivacaftor monotherapy) are different. The summaries and listings of "AE Leading to Treatment Discontinuation" and "AE Leading to Treatment Interruption" account for discontinuation and interruptions for either agent.

9.4.2 Clinical Laboratory

Part A [redacted]

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

The number and percentage of subjects meeting at least 1 threshold analysis criterion event during the TE period will be summarized. The threshold analysis criterion shift from baseline will also be summarized for selected laboratory parameters. The threshold analysis criteria are provided in Appendix F.

Results of urinalysis and the 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.

[redacted]

9.4.3 Electrocardiogram

Part A [redacted]

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

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

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

9.4.4 Vital Signs

Part A [redacted]

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

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

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

[redacted]

[redacted]

9.4.5 Pulse Oximetry

Part A [redacted]

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

The number and percentage of subjects with shift change 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. The reference range for normal oxygen saturation is specified as >95%, and <=95% for low oxygen saturation.

9.4.6 Ophthalmologic Examinations

Part A [redacted]

The ophthalmologic examination results will be presented in individual subject data listings.

9.4.7 Physical Examination

Part A [redacted]

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

[redacted]

[redacted]

10 INTERIM AND DMC ANALYSES

10.1 Interim Analysis

Part A

No interim analysis is planned.

[redacted]

11 REFERENCES

[redacted]

[2] Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 1997;53:983-97.

[3] Lan KK, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70(3):659-63.

[redacted]

[5] 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.

[redacted]

[7] Rubin, DB. and Schenker, N.. Interval estimation from multiply-imputed data: a case study using agriculture industry codes. Journal of the American Statistical Association. 1987; 81: 366–374.

[8] Centers for Disease Control and Prevention. CDC Growth Charts. Available at: http://www.cdc.gov/growthcharts/percentile_data_files.htm.

12 LIST OF APPENDICES

- **Appendix A: Analysis Visit Windows for Safety [redacted] Assessments**

Table 12-1 Analysis Visit Windows for Safety [redacted] Assessments in Part A

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3]
Safety Assessment			
• Serum Chemistry • Hematology	Day 1 (Baseline) Day 8 Day 15 Safety Follow-up	1 8 15 Not applicable	≤1 Pre-dose [1, 12] (12, 29] Use nominal visit
• Standard 12-lead ECG	Day 1 (Baseline) Day 2 Day 15 Safety Follow-up	1 2 15 Not applicable	≤1 Pre-dose [1, 9] (9, 29] Use nominal visit
• Vital Signs	Day 1 (Baseline) Day 2 Day 8 Day 15 Safety Follow-up	1 2 8 15 Not applicable	≤1 [1, 5] (5, 12] (12, 29] Use nominal visit
• Coagulation	Day 1 (Baseline) Day 15	1 15	≤1 Pre-dose [1, 29]
[redacted]			

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

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

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

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

Table 12-3 Prior, Concomitant, and Post Categorization of a Medication

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

P: Prior; C: Concomitant; A: Post

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

- **Appendix C: Details of GLI Equations for Calculating ppFEV1**

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:

Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Quanjer GLI-2012 Regression Equation and Lookup Tables (Version 7 April 2013). Global Lung Function Initiative. [online] Available at: http://www.ers-education.org/home/browse-all-content.aspx?idParent=138978 [Accessed Mar 26, 2018].

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

Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Implementing GLI-2012 regression equations (Version 19 July 2015). Global Lung Function Initiative. [online] Available at: http://www.ers-education.org/home/browse-all-content.aspx?idParent=138979 [Accessed Mar 26, 2018].

Sanja Stanojevic. GLI-2012 - SAS Macro (Version 2, 7 April 2013). Global Lung Function Initiative. [online] Available at: http://www.ers-education.org/home/browse-all-content.aspx?idParent=138988 [Accessed Mar 26, 2018].

Data handling rule for spirometry is as follows:

- Input age and height with at least 2 decimal place
- Height collected at the respective visit should be used; if the height at the respective visit is not available, the last non-missing record will be used.
- For race, map the CRF reported 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 E: 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/assent date, the AE start date will be imputed using the study informed consent/assent 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 first dose date of the Treatment Period;
  - else impute the AE start date as the informed consent/assent date.

Imputation rules for partial AE end date are defined below:

- Impute the AE end date as min (the last day of the month, end of study participation) if day is missing, or min (Dec, end of study participation) if month is missing.

- **Appendix F: Criteria for Threshold Analysis**

Table 12-4 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>20xULN	FDA DILI Guidance
Alkaline Phosphatase	>ULN - ≤1.5xULN >1.5 - ≤2.5xULN >2.5 - ≤5.0xULN >5.0 - ≤20.0xULN >20.0xULN	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	FDA DILI Guidance Jul 2009.

Table 12-4 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
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.
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
Creatine kinase	>ULN - ≤2.5xULN >2.5 - ≤5xULN >5 - ≤10xULN >10xULN	CTCAE grades 1-4
Hematology		
Hemoglobin	Hgb decreased (anemia) <LLN - ≥100 g/L <100 - ≥80 g/L <80 g/L	CTCAE grade 1-3
	Hgb increased >ULN - ≤20 g/L above ULN >20 g/L above ULN - ≤40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3

Table 12-4 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 - ≤1.5xULN >1.5 - ≤2.5xULN >2.5xULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤1.5xULN >1.5 - ≤2.5xULN >2.5 x ULN	CTCAE grade 1-3

Table 12-5 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
HR	Bradycardia ≤50 bpm	
	Tachycardia ≥140 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms	
QTc	Absolute values (ms) >450 ms (Male); >470 ms (Female) ≥500 ms Increase from baseline Increase from baseline 30-60 ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula.

Table 12-6 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
SBP increased	>120 mmHg	
SBP decreased	<70 mmHg	
DBP increased	>80 mmHg	
DBP decreased	<50 mmHg	

Table 12-6 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
Weight	Weight gain ≥5% increase from baseline	
	Weight loss ≥5% decrease from baseline	