TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX21-445-124
(Final Analysis)

A Phase 3 Double-blind, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of ELX/TEZ/IVA in Cystic Fibrosis Subjects 6 Years of Age and Older With a Non-F508del ELX/TEZ/IVA-responsive CFTR Mutation

Author of SAP: [redacted]

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Vertex Pharmaceuticals Incorporated
50 Northern Avenue

Boston, Massachusetts 02210-1862

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFQ-R RD	Cystic Fibrosis Questionnaire- Revised respiratory domain
CFTR	cystic fibrosis transmembrane conductance regulator gene
CI	confidence interval
CPAP	clinical pharmacology analysis plan
CRF	case report form
CSP	clinical study protocol
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
ETT	Early Termination of Treatment
F508del	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FEV_1	forced expiratory volume in 1 second
FVC	Forced vital capacity
GGT	Gamma-glutamyl transferase
GLI	Global Lung Function Initiative
IDMC	Independent Data Monitoring Committee
max	maximum value
MF	minimal function
min	minimum value
MMRM	mixed-effects model for repeated measures
PD	pharmacodynamic, pharmacodynamics
PEx	pulmonary exacerbations
PK	pharmacokinetic, pharmacokinetics

Abbreviation	Definition
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
QTcF	QT interval corrected by Fridericia's formula
RF	residual function
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SwCl	sweat chloride
TE	treatment-emergent
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

3 MODIFICATIONS

3.1 Modifications to the Approved Clinical Study Protocol

Not Applicable.

3.2 Modifications to the Approved Statistical Analysis Plan

Not Applicable.

3.3 Modifications to the Approved IDMC Charter

Not Applicable.

4 INTRODUCTION

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

This SAP (Methods) documents the planned statistical analyses of efficacy endpoints and safety endpoints for the final analysis. Analyses related to sweat chloride will be documented in this SAP. Other PK and PD analyses will be documented separately in the CPAP for the study.

This SAP (Methods) will be finalized and approved prior to data lock and treatment unblinding. Any revisions to the approved SAP prior to data lock will be documented and approved in an amendment to the SAP and deviations from the approved SAP after data lock will be summarized in the CSR.

The Vertex Biometrics Department will perform the statistical analysis for the final analysis and prepare the analysis package for the final analysis; SAS (Version 9.4 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets).

5 STUDY OBJECTIVES

5.1 Primary Objective

To evaluate the efficacy and PD of ELX/TEZ/IVA

5.2 Secondary Objectives

To evaluate safety and tolerability of ELX/TEZ/IVA

6 STUDY ENDPOINTS

6.1 Primary Endpoint

Absolute change from baseline in ppFEV$_1$ through Week 24

6.2 Secondary Endpoints

- Absolute change from baseline in SwCl through Week 24
- Absolute change from baseline in CFQ-R RD score through Week 24
- Absolute change from baseline in BMI at Week 24
- Absolute change from baseline in weight at Week 24
- Number of PEx through Week 24
- Safety and tolerability assessments based on AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry

6.3 Other Endpoints

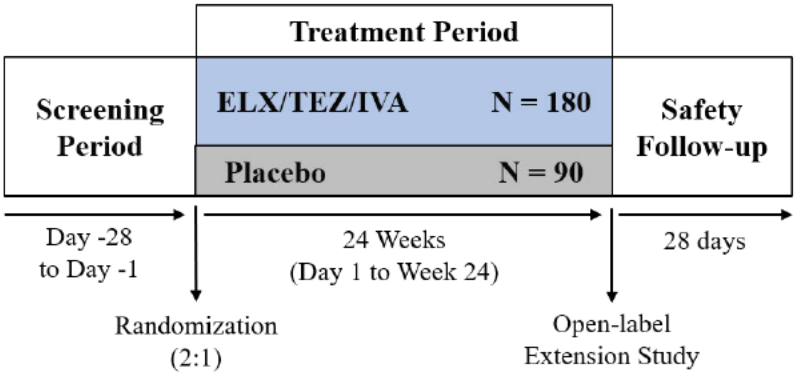
- Absolute change from baseline in BMI z-score (subjects ≤20 years of age) at Week 24
- Absolute change from baseline in weight z-score (subjects ≤20 years of age) at Week 24
- Plasma PK parameters including ELX, TEZ, IVA, and relevant metabolites

7 STUDY DESIGN

7.1 Overall Design

This is a Phase 3, randomized, placebo-controlled, double-blind, parallel group study. Subjects 6 years of age and older with a qualifying non-*F508del* ELX/TEZ/IVA-responsive *CFTR* mutation and no exclusionary mutations may be eligible for enrollment. Qualifying ELX/TEZ/IVA-responsive mutations can be categorized as MF-like and RF-like. MF-like mutations have a clinical phenotype without evidence of residual CFTR function. RF-like mutations result in residual CFTR function. A schematic of the study design is shown in Figure 7-1.

Figure 7-1 Schematic of the Study Design



IVA: ivacaftor; TEZ: tezacaftor; ELX: elexacaftor
Note: The figure is not drawn to scale. The Safety Follow-up Visit is not required for subjects who complete the Week 24 Visit and enroll in an open-label study within 28 days after the last dose of study drug (Section 9.1.3 of protocol).

The ELX/TEZ/IVA dose regimen will be based on the subject's age and weight on Day 1 as shown in Table 7-1; subjects will receive this dose regimen throughout the Treatment Period, regardless of changes in age or weight. ELX/TEZ/IVA will be administered as 2 FDC tablets in the morning and a single IVA monotherapy tablet in the evening regardless of dosing regimen.

Table 7-1 Treatment Period Dosages

Treatment Group Subject Age Weight	ELX Dosage	TEZ Dosage	IVA Dosage
ELX/TEZ/IVA			
≥12 years			
All weights	200 mg qd	100 mg qd	150 mg q12h
≥6 to <12 years			
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
<30 kg	100 mg qd	50 mg qd	75 mg q12h
Placebo			
All ages and all weights	0 mg	0 mg	0 mg

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

Please refer to the Table 3-1 and Table 3-2 of the CSP for more details about study visits and assessments.

7.2 Sample Size and Power

Approximately 270 subjects will be enrolled and randomized (2:1) to the ELX/TEZ/IVA arm or the placebo arm.

The primary endpoint is the absolute change from baseline in $ppFEV_1$ through Week 24. The primary null hypothesis to be tested is that the mean absolute change from baseline in $ppFEV_1$ through Week 24 is the same for the ELX/TEZ/IVA and placebo treatment groups. The null hypothesis will be tested at a 2-sided significance level of 0.05.

Assuming a within group SD of 9 percentage points and a 10% dropout rate at Week 24, a total sample size of 270 subjects (180 subjects in the ELX/TEZ/IVA group and 90 subjects in placebo group) will have approximately 90% power to detect a difference of 4.0 percentage points for the mean absolute change from baseline in $ppFEV_1$ through Week 24 between the 2 treatment groups, based on a 2-sided 2-sample *t*-test at a significance level of 0.05.

7.3 Randomization

Subjects will be randomized 2:1 (ELX/TEZ/IVA group: placebo group). Randomization will be stratified based on $ppFEV_1$ determined during the Screening Period (<70 versus ≥70), age at the Screening Visit (<18 years old versus ≥18 years old) and *CFTR* mutation group (contains ≥ 1 RF-like mutation versus does not contain an RF-like mutation).

7.4 Blinding and Unblinding

Refer to the CSP section 10.7 for details.

7.5 Interim Analysis

No Interim Analysis was planned for this study.

8 ANALYSIS SETS

8.1 All Subjects Set

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

8.2 Full Analysis Set

The **Full Analysis Set** (FAS) will include all randomized subjects who carry the intended mutation and received 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 in which subjects will be analyzed according to their randomized treatment group, unless otherwise specified.

8.3 Safety Set

The **Safety Set** will include all subjects who received at least 1 dose of study drug. The Safety Set will be used for all safety analyses in which subjects will be analyzed according to the treatment they received, unless otherwise specified. If a subject received study drug from both

the placebo group and the treatment group, the subject will be analyzed in the Safety Set of the treatment group.

9 STATISTICAL ANALYSIS

This section discusses the analyses planned for the final analysis.

9.1 General Considerations

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, SD, median, min, and max.

Categorical variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place.

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

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

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

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

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

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

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

Incomplete/missing data will not be imputed, unless otherwise specified.

Outliers: No formal statistical analyses will be performed to detect or remedy the presence of statistical outliers, unless otherwise specified.

9.2 Background Characteristics

9.2.1 Subject Disposition

The number of subjects in the following categories will be summarized:

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

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

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

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

9.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group and overall 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 (North America and Europe)

Baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- BMI z-score (for subjects ≤20 years old at Baseline)
- Weight z-score (for subjects ≤20 years old at Baseline)

Stratification categories will include the following:

- Age at the Screening Visit (<18, and ≥18 years)
- $ppFEV_1$ at the Screening Visit (<70 and ≥70)

- *CFTR* mutation group (contains ≥ 1 RF-like mutation versus does not contain an RF-like mutation)

Disease characteristics will include the following:

- $ppFEV_1$ at baseline (≥ 40 to <70, ≥70 to ≤90, and >90)
- $ppFEV_1$ at baseline (continuous)
- Sweat chloride at baseline (continuous)
- CFQ-R respiratory domain score at baseline (continuous)
- Prior use of dornase alfa (Yes, No)
- Prior use of azithromycin (Yes, No)
- Prior use of inhaled antibiotic (Yes, No)
- Prior use of any bronchodilator (Yes, No)
- Prior use of any inhaled bronchodilator (Yes, No)
- Prior use of any inhaled hypertonic saline (Yes, No)
- 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.

9.2.3 Medical History

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

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

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

Prior medication: any medication that was administered during the 56 days before the first dose of study drug.

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

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

A given medication may be classified as 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/stop date and if 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. Details for imputing missing or partial start and/or stop dates of medication are described in Appendix B.

Prior medications and concomitant medications will be summarized descriptively for FAS using frequency tables by: 1) treatment group and overall, preferred name (PN); and 2) treatment group and overall, Anatomical Therapeutic Chemical class (ATC) level 1, ATC level 2, and PN.

Post-treatment medications will be listed in all medication listing.

9.2.5 Study Drug Exposure

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

Study drug exposure (in weeks) will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized by interval: ≤1 week, >1 to ≤2 weeks, >2 to ≤4 weeks, >4 to ≤8 weeks, >8 to ≤12 weeks, >12 to ≤16 weeks, >16 to ≤20 weeks, >20 to ≤24 weeks, and >24 weeks using counts and percentages. Additionally, the total study drug exposure, defined as the sum total of the study drug exposure across all subjects (in patient-weeks and patient-years), will be provided.

Exposure summaries will be based on the Safety Set and presented by treatment group and overall.

9.2.6 Study Drug Compliance

Study drug compliance will be summarized by treatment group and overall 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 on that day. A study drug interruption that continues through the end of the study participation (i.e., subject does not resume study drug before the end of the study participation) will not be included in the compliance calculation.

Percentage of study drug compliance will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max and based on the FAS, and presented by treatment group and overall. It will also be summarized in categories: <80% and ≥80% using frequency tables.

9.2.7 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. A protocol deviation review team will categorize IPDs according to the Protocol Deviation Plan during the study.

IPDs will be provided in an individual subject data listing. A summary table of IPDs based on the FAS will also be provided.

9.3 Efficacy Analysis

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

9.3.1 Analysis of Primary Efficacy Endpoint

9.3.1.1 Definition of Variables

The primary efficacy variable is the absolute change in $ppFEV_1$ from baseline through Week 24. Percent predicted FEV_1 is the ratio of FEV_1 (L) and predicted FEV_1 (L), expressed as a percentage. See Appendix C for more details.

9.3.1.2 Primary Analysis

The primary analysis will be performed using a MMRM with change from baseline at Day 15, Week 4, Week 8, Week 16, and Week 24 as the dependent variable. The model will include treatment group, visit, and treatment by visit interaction as fixed effects, with continuous baseline $ppFEV_1$, age at screening (<18 versus ≥18 years of age) and mutation group (contains ≥ 1 RF-like mutation versus does not contain an RF-like mutation) as covariates. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the *F*-test for fixed effects will be estimated using the Kenward-Roger approximation[2]. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, a compound symmetry covariance structure will be used instead. Conditional on the observed data and covariates, missing data will be assumed to be missing at random.

The primary result obtained from the model will be the estimated treatment difference through Week 24, defined as the averaged treatment effects estimated at Week 4, Week 8, Week 16, and Week 24. The adjusted means with 2-sided 95% CIs and 2-sided *P* value will be provided. Furthermore, the treatment difference at each post-baseline visit obtained from the model will also be provided.

The estimated within group change from baseline and treatment difference at each post-baseline visit, obtained from the model, will be provided. The estimated within group change and its SE at each post-baseline visit will also be plotted by treatment group. In addition, the post-baseline raw values and the absolute change from baseline at each post-baseline visit will be summarized descriptively (n, mean, SD, median, minimum, and maximum).

9.3.1.3 Supportive Analyses

There will be no supportive analysis for the primary efficacy endpoint.

9.3.1.4 Sensitivity Analyses

MMRM based on Multiple Imputation (MI)

An underlying assumption of the MMRM method is that data are missing at random. To minimize the amount of missing data, subjects who prematurely discontinue study drug treatment will continue to complete all scheduled study visits for spirometry and other efficacy assessments.

To assess the impact of missing data and the assumption that data are missing at random, a multiple imputation algorithm will be used if at least 10% of the subjects have missing changes

in ppFEV1 at Week 24 in any treatment group. Missing absolute change from baseline in ppFEV1 assessments will be imputed starting from the first visit with missing values, for which all subsequent visits through Week 24 are also missing. For intermediate missing data, i.e., missing values that fall between two non-missing ones, it is reasonable to assume that they are missing at random and therefore will not be imputed. An MMRM analogous to that for the primary analysis of the primary endpoint will be applied to each imputed dataset and the relevant MI estimators will be reported. Details for the MI steps are presented in Appendix D.

9.3.1.5 Subgroup Analysis

Subgroup analyses of the primary efficacy endpoint will be performed using a model similar to that of the primary analysis for each of the following subgroups.

- Age at Screening (<18, ≥18 years)
- $ppFEV_1$ at baseline (< 70, ≥ 70)
- Sex (male, female)

The MMRM used for the primary analysis will be used for the subgroup analysis, where the same model will be applied to each category of the subgroup. Note that for the subgroup analysis based on age, the covariate of age at screening (<18 versus ≥18 years of age) from the MMRM will be removed. The adjusted means with 2-sided 95% CIs will be provided. Furthermore, estimated between group difference through Week 24 within a subgroup will also be presented in a forest plot. Note: Due to potential small sample size, the results from above mentioned subgroup analysis should be interpreted with caution.

9.3.2 Analysis of Secondary Endpoints

9.3.2.1 Definition of Variables

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 sweat volume ≥15 µL is required for an accurate determination of sweat chloride. Any results reported as having sweat volume <15 µL or SwCl values reported as >160 mmol/L, will be considered missing. Any sweat chloride values reported as <10 mmol/L will be imputed as 10 mmol/L.

CFQ-R: The CFQ-R[1,3,5] is a validated CF-specific instrument that measures quality-of-life domains. This study utilizes four different versions of CFQ-R:

CFQ-R for Children ages 6 to 11

CFQ-R for Children ages 12 and 13

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

CFQ-R for Parents/Caregivers (subjects 13 years and younger)

In all four versions, specific question belonging to a domain is scored 1, 2, 3, or 4. The CFQ-R domain score, e.g., physical domain score or respiratory domain score, is defined as a scaled score as follows:

Scaled score for a domain = 100 × (mean (scores of all questions in the domain) − 1)/3,

where the score from a negatively phrased question is first reversed, i.e., reversed score = 5 – actual score, so that 1 always represents the worst condition and 4 the best condition. The (scaled) domain score ranges from 0 (worst condition) to 100 (best condition). The scaled score for a specific domain will not be calculated if more than half of the questions in the domain have missing scores.

The (scaled) domain score from the CFQ-R for Children ages 6 to 11, for Children ages 12 and 13 and for Adolescent and Adults will be pooled for the analysis purpose.

BMI: the BMI at each visit is calculated using the weight and height at each visit as follows:

$$BMI = \frac{\text{Weight (kg)}}{\text{Height}^2\ (\text{m}^2)}$$

PEx: A PEx is defined as a new event or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the following signs/symptoms:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature above 38°C (equivalent to approximately 100.4°F)
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in PE of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

The **PEx analysis period** will include the time from the first dose date of study drug in the treatment period until the last efficacy assessment. For subjects with a Week 24 Visit, the last efficacy assessment will be the Week 24 visit. For subjects who do not have a Week 24 Visit, the last efficacy assessment will be the earlier of Day 169 and the end of study participation.

The number of PEx through Week 24 is then defined as the total number of PEx for each treatment group during the PEx analysis period.

9.3.2.2 Analysis Method

Absolute change in SwCl from baseline through Week 24: The analysis of absolute change from baseline in SwCl through Week 24 will be based on an MMRM similar to the analysis of the primary endpoint above, with absolute change from baseline in SwCl at Day 15, Week 4, Week 8, Week 16, and Week 24 as the dependent variable.

The primary result obtained from the model will be the estimated treatment difference through Week 24, defined as the averaged treatment effects estimated at Week 4, Week 8, Week 16, and Week 24. The adjusted mean with a 2-sided 95% CI and a 2-sided *P* value will be provided.

The estimated within group change from baseline and treatment difference at each post-baseline visit, obtained from the model, will be provided. The estimated within group change and its SE at each post-baseline visit will also be plotted by treatment group. In addition, the post-baseline raw values and the absolute change from baseline at each post-baseline visit will be summarized descriptively (n, mean, SD, median, minimum, and maximum).

Absolute change from baseline in CFQ-R Respiratory Domain (RD) score through Week 24: Analysis of this domain will be based on an MMRM similar to the analysis of the primary efficacy variable. Data obtained from Week 4, Week 8, Week 16, and Week 24 Visits will be included in the model to estimate the treatment effect through Week 24. Plot and summary tables similar to those for $ppFEV_1$ and SwCl will be provided.

Absolute change from baseline in BMI at Week 24: Analysis of this variable will be based on an MMRM similar to the analysis of the primary efficacy variable. Data obtained from Day 15, Week 4, Week 8, Week 16, and Week 24 Visits will be included in the model. Plot and summary tables similar to those for $ppFEV_1$ and SwCl will be provided.

Absolute change from baseline in weight at Week 24: Analysis of this variable will be based on an MMRM similar to the analysis of the primary efficacy variable. Data obtained from Day 15, Week 4, Week 8, Week 16, and Week 24 Visits will be included in the model. Plot and summary tables similar to those for $ppFEV_1$ and SwCl will be provided.

Number of PEx through Week 24: The number of PEx during the PEx analysis period will be performed using a negative binomial regression model with a fixed effect for treatment, as well as continuous baseline $ppFEV_1$, age at screening (<18 versus ≥18 years of age) and mutation group (contains ≥ 1 RF-like mutation versus does not contain an RF-like mutation) as covariates. The logarithm of the subject-specific PEx analysis period duration (in years) will be treated as the offset in the model. The estimated rate ratio and the associated 2-sided 95% CI and 2-sided p-value will be provided. If model does not converge, alternative models (e.g., a Poisson model with the same covariates) might be used instead.

9.3.2.3 Multiplicity Adjustment

The secondary endpoints will be formally tested at an alpha of 0.05 at the final analysis when all subjects complete study participation. A hierarchical testing procedure will be used to control the type I error rate for the multiple secondary endpoints tested at an alpha of 0.05. For a test at any step to be considered statistically significant within the testing hierarchy, it must be statistically significant, and all previous tests (if any) within the hierarchy must be statistically significant at the 0.05 level. The testing order of the secondary endpoints is as follows:

1. First secondary endpoint: Absolute change in SwCl from baseline through Week 24
2. Second secondary endpoint: Absolute change in CFQ-R respiratory domain from baseline through Week 24
3. Third secondary endpoint: Absolute change in BMI from baseline at Week 24
4. Fourth secondary endpoint: Absolute change in weight from baseline at Week 24

5. Fifth secondary endpoint: Number of PEx through Week 24

9.3.3 Analysis of Other Endpoints

9.3.3.1 Definition of Variables

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

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

9.3.3.2 Analysis Method

Absolute change from baseline in BMI z-score at Week 24 (for subjects ≤20 years of age at Baseline): Analysis of this variable will be based on an MMRM similar to the analysis of the primary efficacy variable, excluding the covariate of age at screening (<18 versus ≥18 years of age), for subjects ≤20 years of age at Baseline. Data obtained from Day 15, Week 4, Week 8, Week 16, and Week 24 Visits will be included in the model. Plot and summary tables similar to those for ppFEV$_1$ and SwCl will be provided.

Absolute change from baseline in Weight z-score at Week 24 (for subjects ≤20 years of age at Baseline): Analysis of this variable will be based on an MMRM similar to the analysis of the primary efficacy variable, excluding the covariate of age at screening (<18 versus ≥18 years of age), for subjects ≤20 years of age at Baseline. Data obtained from Day 15, Week 4, Week 8, Week 16, and Week 24 Visits will be included in the model. Plot and summary tables similar to those for ppFEV$_1$ and SwCl will be provided.

9.3.4 Analysis of Additional Efficacy Variables

9.3.4.1 Analysis of Additional Spirometry Variables

Summary statistics for raw values and for changes from baseline of the following spirometry measurements will be presented by treatment group at each visit:

- FEV$_1$:
  - Absolute change from baseline in FEV$_1$ (L)
  - Relative change from baseline in FEV$_1$ (%)
  - Absolute change from baseline in percent predicted FEV$_1$ (percentage points)
  - Relative change from baseline in percent predicted FEV$_1$ (%)
- FVC:
  - Absolute change from baseline in FVC (L)
  - Relative change from baseline in FVC (%)
  - Absolute change from baseline in percent predicted FVC (percentage points)
  - Relative change from baseline in percent predicted FVC (%)

- $FEF_{25-75\%}$:
    - Absolute change from baseline in $FEF_{25-75\%}$ (L/sec)
    - Relative change from baseline in $FEF_{25-75\%}$ (%)
    - Absolute change from baseline in percent predicted $FEF_{25-75\%}$ (percentage points)
    - Relative change from baseline in percent predicted $FEF_{25-75\%}$ (%)
- FEV_1/FVC:
    - Absolute change from baseline in FEV_1/FVC
    - Relative change from baseline in FEV_1/FVC (%)
    - Absolute change from baseline in percent predicted FEV_1/FVC
    - Relative change from baseline in percent predicted FEV_1/FVC (%)

9.3.4.2 Analysis of Other CFQ-R Variables

Absolute change in the CFQ-R non-respiratory domain score from baseline through Week 24: Analysis of this domain(s) will be based on an MMRM similar to the analysis of the primary efficacy variable. Data obtained from Week 4, Week 8, Week 16, and Week 24 Visit will be included in the model and all these visits will be included in the estimation of the average treatment effect through Week 24. Summary tables similar to those for $ppFEV_1$ and SwCl will be provided.

9.3.5 Additional Analysis

For all subjects (pooled together) with any of these mutations 2789+5G>A, 3272-26A>G, and 3849+10kbC>T, the absolute change from baseline through Week 24 in the following efficacy endpoints:

- $ppFEV_1$
- SwCl
- CFQ-R RD

will be summarized descriptively (n, mean, SD, median, minimum, maximum, and 95% CI). These analyses will also be conducted for all subjects (pooled together) with any of these mutations: P5L, R117C, L206W, V232D, T338I, R347H, A455E, S945L, L997F, R1066H, D1152H, G85E, R347P, L1077P, and M1101K.

9.3.6 Remote Measures in Extenuating Circumstances

CSP Section 9.1.7 states that, under extenuating circumstances, remote measures may be implemented (e.g., if a subject is unable to travel to the study site due to safety concerns and/or local restrictions related to COVID-19 or other emerging events). Such measures, pertaining to spirometry, will be listed if available.

9.4 Safety Analysis

All safety analyses will be based on data from the TE period. Subjects will be analyzed according to the treatment they received in the Treatment Period. For subjects receiving study drug from more than one treatment group, the treatment group allocation will ELX/TEZ/IVA.

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

- TEAEs
- Clinical laboratory values
- ECGs
- Vital signs
- Pulse oximetry
- Ophthalmologic examination

Only descriptive analysis of safety will be performed. No statistical testing will be performed.

9.4.1 Adverse Events

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

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

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

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

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

Details for imputing missing or partial start dates of AEs are described in Appendix E.

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 3/4/5 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 3/4/5 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 SOC and 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 for TEAEs showing number and percentage of subjects

- All TEAEs by PT
- All Related 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 3/4/5 TEAEs, SAEs and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.

9.4.2 Clinical Laboratory

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 by treatment group.

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

For select LFT laboratory tests (ALT, AST, 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.

Results of positive urine/serum pregnancy test will be listed in individual subject data listings only. For positive serum pregnancy listing, subjects with serum hCG above the upper limit of normal will be selected.

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

9.4.3 Electrocardiogram

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

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

9.4.4 Vital Signs

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

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

9.4.5 Pulse Oximetry

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

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

9.4.6 Ophthalmologic Examinations

The ophthalmologic examination results will be conducted only for subjects who are <18 years of age on the date of informed consent and presented in individual subject data listings only.

9.4.7 Physical Examination

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

9.4.8 COVID-19 Impacted Visits

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

9.4.9 Supportive Safety Analysis

9.4.9.1 Adverse Events of Special Interest

For this study, elevated transaminases events and rash events, as determined by MedDRA preferred terms in the respective Customized MedDRA Queries (CMQ), are considered as adverse events of special interest.

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

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

In addition, for treatment-emergent rash events, these categories will be summarized for the following subgroups:

- Sex (male, female)
- Female subjects with concomitant hormonal therapy (Yes, No)

9.4.9.2 Hormonal Therapy

The number of subjects who used hormonal therapy concomitantly will be summarized by treatment group based on the Safety Set.

10 SUMMARY OF Interim and IDMC ANALYSIS

10.1 Interim analysis

No interim analysis is planned for this study.

10.2 IDMC Analysis

The IDMC's objectives and operational details are defined in a separate document (IDMC Charter) which was finalized before the first subject was screened in the study. The IDMC's planned safety reviews of study data are outlined in the IDMC Charter and IDMC SAP.

11 REFERENCES

[1] Goss C, Quittner AL. Patient-reported outcomes in cystic fibrosis. Proc Am Thorac Soc. 2007;4:1-9.

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

[3] Modi AC, Quittner AL. Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis. J Pediatr Psychol. 2003;28(8):535-45.

[4] 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.

[5] Quittner AL, Modi A, Cruz I. Systematic review of health-related quality of life measure for children with respiratory conditions. Pediatr Respir Rev. 2008;9:220-32.

[6] 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.

[7] 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 and Efficacy Assessments

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

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2,3,4]
Safety Assessment			
Serum Chemistry Hematology Standard 12-lead ECG Vital Signs (excluding BMI, Weight, Height and their Z-scores)	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 16 Week 24 Safety Follow-up	1 15 29 57 113 169 Not applicable	≤1 Pre-dose [1, 22] (22, 43] (43, 85] (85, 141] (141, 183] Use nominal visit
Coagulation	Day 1 (Baseline) Week 24 Safety Follow-up	1 169 Not applicable	≤1 Pre-dose [1, 183] Use nominal visit
Efficacy Assessment			
Spirometry, Weight, Height and BMI (and the corresponding z-score) [5]	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 16 Week 24 Safety Follow-up	1 15 29 57 113 169 Not applicable	≤1 Pre-dose (1, 22] (22, 43] (43, 85] (85, 141] (141, 183] >183
Sweat Chloride	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 16 Week 24	1 15 29 57 113 169	≤1 Pre-dose (1, 22] (22, 43] (43, 85] (85, 141] (141, 183]
CFQ-R[5]	Day 1 (Baseline) Week 4 Week 8 Week 16 Week 24 Safety Follow-up	1 29 57 113 169 Not applicable	≤1 (1, 43] (43, 85] (85, 141] (141, 183] >183

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

[2] The analysis visit windows will be applied using the following rules for both scheduled and unscheduled visits:
a. If no numerical measurement is available within a visit window, the measurement will be considered missing for the visit.
b. If there is more than 1 numerical measurement available within a visit window, use the following rules:
   i. The measurement closest to the target day will be used; or
   ii. If there are multiple measurements with the same distance from the target day, the latest measurement will be used. If the latest measurement cannot be determined, then unscheduled visit will be selected.

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

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

[3] For measurements collected on the date of first dose of study drug, if it cannot be determined whether the measurement is before or after the first dose:

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

[4] For safety Assessment, Safety Follow-up analysis visit will be based on nominal Safety Follow-up visit. If a subject doesn't have a nominal Safety Follow-up visit but has an ETT visit with study day >183, then the ETT visit will be mapped into Safety Follow-up analysis visit.

[5] For efficacy analysis, if there are multiple assessments >183, then nominal Safety Follow-up visit will be mapped to Safety Follow-up visit. If there is only ETT assessment > 183, the ETT visit will be mapped to the Safety Follow-up visit;else if there are multiple assessments with >183 then select the earliest record.

Derived Variables:

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

   Obtain age at informed consent (in days) in yy mm format (e.g., 24 years, 6 months) from screening vital signs page, and add 0.5 month to convert to days.

   Obtain informed consent date .

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

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

   Obtain age at informed consent (in months) in yy mm format (e.g., 24 years, 6 months) from screening vital signs page.

   Obtain informed consent date.

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

3. Missing first dose date or last dose date

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

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

4. Sweat Chloride:

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

5. Electrocardiogram:

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

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

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

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

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date (in practice, 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 practice, use the End of Study Date to impute).

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

Table 12-2 Logic for determining the Category 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 ppFEV$_1$

Percent predicted values will be calculated for parameters of FEV_1, FVC, FEV_1/FVC, and $FEF_{25\%-75\%}$ 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 Jul. 9, 2019].

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 Jul. 9, 2019].

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 Jul. 9, 2019].

Data handling rule for spirometry is as follows:

- Input age with at least 2 decimal place
- Use height at screening regardless if height is collected at other study visits for subjects whose age at informed consent is >21 years. For subjects with age <=21 years, height collected at the respective visit should be used.
- For race, map CRF black or AA 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: Steps for Multiple Imputation

For the multiple imputation (MI) to be applied to the MMRM for the sensitivity analysis of the primary efficacy endpoint, the following steps will be followed:

Imputation distribution

The imputation distribution for the missing absolute change from baseline in $ppFEV_1$ at visit *t* will be a normal distribution. All subjects in the corresponding analysis set (e.g., FAS) will be classified into one of three categories based on the following rules:

- Non-missing category: Subjects who have a $ppFEV_1$ assessment at the last timepoint of the dependent variable. Given the primary analysis method, this corresponds to the subjects who have a non-missing absolute change from baseline in $ppFEV_1$ at Week 24.
- Missing category 1: Subjects with missing absolute change from baseline in $ppFEV_1$ at the last timepoint of the dependent variable (Week 24), who discontinued treatment because of AEs, noncompliance with study drug, death, or physician decision, or because the subject refused further dosing or required prohibited medication.
- Missing category 2: Subjects with missing absolute change from baseline in $ppFEV_1$ at the last timepoint of the dependent variable (Week 24), who completed the protocol-specified treatment or discontinued treatment for any reason not listed in Category 1.

Imputation algorithm

We will use the following algorithm that relates the mean of the missing absolute change from baseline in $ppFEV_1$ at visit *t* to the missing categories defined above. The algorithm will be implemented within each treatment group as follows:

- Missing category 1: randomly draw a sample from the normal distribution (μ_{25}, σ^2), where μ_{25} is the 25th percentile of the non-missing absolute changes from baseline in $ppFEV_1$ at visit *t* and σ^2 the sample variance estimated using the non-missing absolute changes at visit *t*.
- Missing category 2: randomly draw a sample from the normal distribution (μ, σ^2), where μ is the mean of the non-missing absolute changes from baseline in $ppFEV_1$ at visit *t* and σ^2 is the sample variance estimated using the non-missing absolute changes at visit *t*.

Analysis model

The complete MI method is described below:

- Form an "imputed dataset" by imputing missing values at each visit for those subjects who have a missing value at the visit and have all subsequent values missing. The appropriate normal distribution specified in the algorithm above will be used for each such subject, based on their category.
- Repeat this process *K* (*K*=20) times to form *K* imputed datasets.
- Fit the same MMRM model as the one used for primary analysis to each imputed dataset to estimate the absolute change at Week 4.
- Combine the results from the analyses of *K* imputed datasets using the SAS procedure MIANALYZE to derive the MI estimator.

Let θ be the true treatment difference. Denote by $\tilde{\theta}_k$ the estimate of θ from the k^{th} imputed dataset, and the corresponding estimate of the variance is denoted by V_k. The MI estimator of θ, $\tilde{\theta}_{\text{MI}}$, is the average of the K individual estimates.

The estimated variance of $\tilde{\theta}_{\text{MI}}$ is a combination of the between- and within-imputation variability as follows: $V_{\text{MI}} = W + \left(1 + \frac{1}{K}\right) B$, where $W = \frac{1}{K}\sum_{k=1}^{K} V_k$ is the within-imputation variability and is $B = \frac{1}{K-1}\sum_{k=1}^{K}(\tilde{\theta}_k - \tilde{\theta}_{\text{MI}})^2$ is the between-imputation variance. The statistic $T = \frac{\tilde{\theta}_{\text{MI}} - \theta}{\sqrt{V_{\text{MI}}}}$ has an approximate t_V distribution[7], where $V = (K-1)(1 + \frac{W}{B})^2$.

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 informed consent date, the AE start date will be imputed using the 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.
    - 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 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.
    - For the IDMC purpose, if the end of study participation date is missing, then the IDMC data cutoff date will be used instead in the imputation

Appendix F: Criteria for Threshold Analysis

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

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

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

Parameter	Threshold Analysis	Comments
GGT	>ULN - ≤ 2.5xULN >2.5 – ≤ 5.0xULN >5.0 – ≤ 20.0xULN >20.0xULN	CTCAE grade 1-4
Clinical Chemistry (NON-LFT)		
Albumin	<LLN - ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>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
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

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

Parameter	Threshold Analysis	Comments
Reticulocytes/Erythrocytes (%)	<LLN >ULN	No CTCAE
Coagulation		
Activated partial thromboplastin time (PTT)	>ULN - ≤ 1.5 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 12-4 Threshold Analysis Criteria for ECGs

Thresholds for Subjects Aged 6 to 11 Years Old at Baseline		
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.
Thresholds for Subjects Aged 12 and Older at Baseline		
Parameter	**Threshold Analysis**	**Comments**
HR	Bradycardia <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	Per HV grade 2, 3, plus shift change

Table 12-4 Threshold Analysis Criteria for ECGs

	Tachycardia	Per HV grade 1, 2, 3, plus shift change
	>100 bpm	
	>115 bpm	
	>130 bpm	
	Increase from baseline ≥10 bpm	
	Increase from baseline ≥20 bpm	
	>100 bpm and increase from baseline ≥10 bpm	
	>100 bpm and increase from baseline ≥20 bpm	
PR	≥240 ms	
	≥300 ms	
	≥200 ms and increase from baseline ≥40 ms	
	≥200 ms and increase from baseline ≥100 ms	
QRS	>110 ms	
	>160 ms	
	Increase from baseline ≥20 ms	
	Increase from baseline ≥40 ms	
QTc		To be applied to any kind of QT correction formula.
	>450 to <500ms (Male) or >470 to <500ms (Female)	
	≥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	

Note: Based on CPMP 1997 guideline.

Table 12-5 Threshold Analysis Criteria for Vital Signs

Thresholds for Subjects Aged 6 to 11 Years Old at Baseline		
Parameter	**Threshold Analysis**	**Comments**
SBP	>120 mmHg	
	<70 mmHg	
DBP	>80 mmHg	
	<50 mmHg	
Weight	Weight gain ≥5% increase from baseline	
	Weight loss ≥5% decrease from baseline	
Thresholds for Subjects Aged 12 and Older at Baseline		
Parameter	**Threshold Analysis**	**Comments**
Pulse Rate	Same as ECG category for Subjects Aged 12 and Older at Baseline	
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

Table 12-5 Threshold Analysis Criteria for Vital Signs

SBP decrease		Per HV grade 1, 3, plus shift change
	<90 mmHg	
	<80 mmHg	
	>10 mmHg decrease from baseline	
	>20 mmHg decrease from baseline	
	<90 mmHg and >10 mmHg decrease from baseline	
	<90 mmHg and >20 mmHg decrease from baseline	
	<80 mmHg and >10 mmHg decrease from baseline	
	<80 mmHg and >20 mmHg decrease from baseline	
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	

Table 12-5 Threshold Analysis Criteria for Vital Signs

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