VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX18-445-106, Version 3.0

A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-445/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age

Author of SAP: [redacted]

Version: 3.0
Version Date of SAP: 11 August 2020

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

1 TABLE OF CONTENTS

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
CFQ-R	Cystic Fibrosis Questionnaire – Revised
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
ELX	elexacaftor
FAS	full analysis set
FDC	fixed-dose combination
$FEF_{25-75\%}$	forced expiratory flow, midexpiratory phase
FEV_1	forced expiratory volume in 1 second
[redacted]	[redacted]
FVC	forced vital capacity
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
MFHS	modified facial hedonic scale
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

Abbreviation	Term
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
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 VX18-445-106 (Study 445-106) is a Phase 3, 2-part (Parts A and B), multicenter study evaluating the pharmacokinetics (PK), safety, and tolerability of elexacaftor (ELX, VX-445) 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 445-106 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. Selected analyses related to sweat chloride will be documented in this SAP. PK and PD (if applicable) analyses will be documented separately in the clinical pharmacology analysis plan (CPAP) for the study.

Due to the outbreak of COVID-19, to ensure continued safety of subjects who *cannot* travel to the study sites for their visits (for any reason due to COVID-19), specific alternative measures are being implemented to minimize the risk of exposure to COVID-19. This SAP summarizes the additional statistical analyses that are related to these alternative measures including but not limited to spirometry assessments using the Air Next device and obtained in the home, home assessed Cystic Fibrosis Questionnaire – Revised (CFQ-R), home assessed Modified Facial Hedonic Scale (MFHS), and additional data collected during the unscheduled visits that occurred to perform assessments that had been missed at the time of the Week 24 visit.

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 original SAP (version 1.0) was based on CSP Version 1.0 and finalized and approved prior to the data lock for Part A. The SAP amendment (version 2.0) was finalized and approved to incorporate changes in the CSP Version 3.0. This SAP amendment (version 3.0) will be finalized and approved prior to the data lock for Part B. Any revisions to the approved SAP amendment, if applicable, will be documented and approved in an additional amendment to the SAP.

5 STUDY OBJECTIVES

5.1 Primary Objectives

Part A

To evaluate the PK of ELX, TEZ, and IVA when dosed in TC

Part B

To evaluate the safety and tolerability of ELX/TEZ/IVA through Week 24

5.2 Secondary Objectives

Part A

- To evaluate the PK of ELX, TEZ and IVA metabolites
- To evaluate the safety and tolerability of ELX/TEZ/IVA

Part B

- To evaluate the efficacy of ELX/TEZ/IVA through Week 24
- To evaluate the PK of ELX, TEZ, and IVA
- To evaluate the PK of ELX, TEZ and IVA metabolites

6 STUDY ENDPOINTS

6.1 Primary Endpoint

Part A

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

Part B

Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, standard 12-lead ECGs, vital signs, pulse oximetry, and ophthalmologic examinations

6.2 Secondary Endpoints

Part A

- PK parameters of ELX, 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

Part B

- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline through Week 24
- Absolute change in sweat chloride (SwCl) from baseline through Week 24
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline through Week 24
- Absolute change in body mass index (BMI) and BMI-for-age z-score from baseline at Week 24
- Absolute change in weight and weight-for-age z-score from baseline at Week 24
- Absolute change in height and height-for-age z-score from baseline at Week 24
- Drug acceptability assessment using Modified Facial Hedonic Scale
- Number of pulmonary exacerbations (PEx) and CF-related hospitalizations through Week 24

- PK parameters of ELX, TEZ, IVA, and relevant metabolites
- Absolute change in lung clearance index$_{2.5}$ (LCI$_{2.5}$) from baseline through Week 24

[redacted]

7 STUDY DESIGN

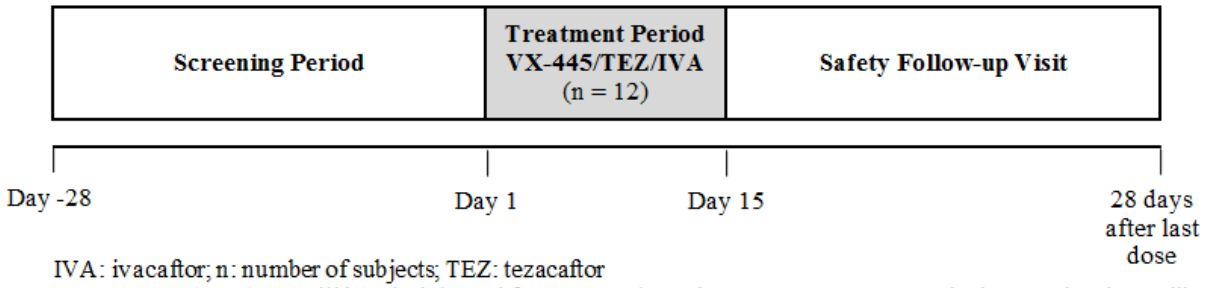
7.1 Overall Design

This is a Phase 3, 2-part (Parts A and B), multicenter study evaluating the PK, safety, and tolerability of ELX/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 ELX/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 to confirm or adjust the dose(s) chosen for Part B. Additional subjects may be enrolled as needed in Part A, based on emerging PK data, to confirm the dose(s) for Part B. Subjects who participate in Part A may participate in Part B.

Figure 7-1 Part A Study Design



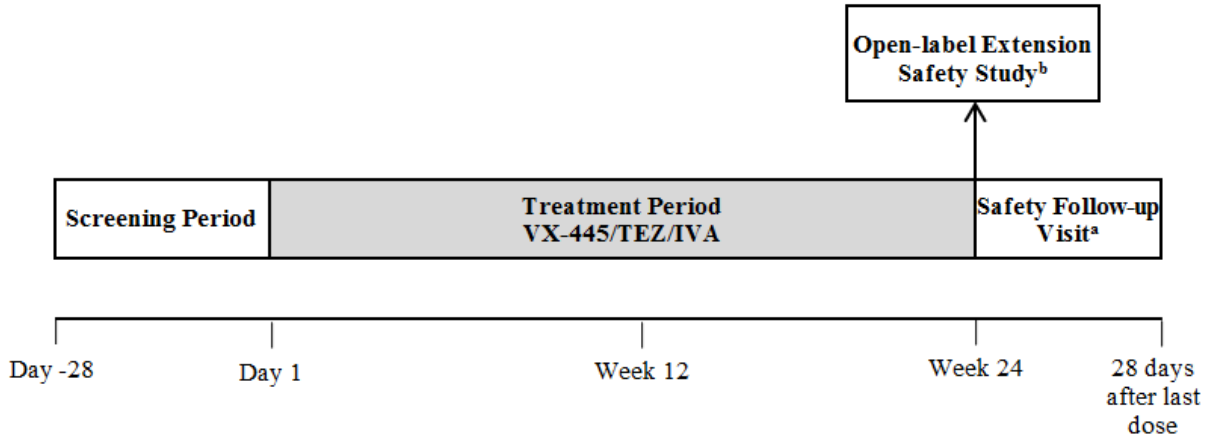
IVA: ivacaftor; n: number of subjects; TEZ: tezacaftor
[a] VX-445/TEZ/IVA will be administered from Day 1 through Day 15. On Day 15, only the morning dose will be administered.

Part B

A schematic of the study design for Part B is provided in Figure 7-2. Part B will initiate after completion of the internal Vertex team's review of available data in Part A that will confirm or adjust the dose(s) to be evaluated in Part B. Approximately 56 subjects (F/F or F/MF genotypes) are planned for enrollment to ensure approximately 45 subjects complete Part B. Approximately 25 subjects with F/MF genotypes and approximately 20 subjects with F/F genotypes are targeted for enrollment in Part B. During the Treatment Period, subjects will be administered ELX/TEZ/IVA for approximately 24 weeks.

Subjects who complete the Part B Treatment Period and have not permanently discontinued study drug will be offered the opportunity to enroll in an optional open-label extension safety study (enrollment will be based on the eligibility criteria specified within the Open-label Extension Safety Study protocol).

Figure 7-2 Part B Study Design



IVA: ivacaftor; TEZ: tezacaftor
[a] The Safety Follow-up Visit is scheduled to occur 4 weeks (± 7 days) after the last dose. This visit is not required for subjects who enroll in an optional open-label extension safety study within 28 days of the last dose.
[b] Subjects who complete the visits in the Treatment Period, regardless of whether they are on a treatment interruption, will be offered the opportunity to enroll in an optional open-label extension safety study evaluating VX-445 in a triple combination regimen.

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

Table 7-1 Part A and Part B Doses

Subjects Weight	ELX Dose	TEZ Dose	IVA Dose
Part A			
All subjects	100 mg qd	50 mg qd	75 mg q12h
Part B			
<30 kg	100 mg qd	50 mg qd	75 mg q12h
≥30 kg	200 mg qd	100 mg qd	150 mg q12h

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

7.2 Sample Size and Power

Part A

Approximately 12 subjects will be enrolled in Part A. Sample size calculations were determined based on ELX 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 ELX.

Part B

The planned enrollment is approximately 56 subjects. Approximately 45 subjects are expected to complete Part B. Incidence of AEs is a safety endpoint. Table 7-2 presents estimates of the probability for observing at least 1 subject with an AE for the given incidence (θ) and sample size. The study will have at least 90% chance of observing an AE in at least 1 subject if the true incidence rate is 5%; and a >95% chance of observing an AE in at least 1 subject if the true incidence rate is 10%. The probabilities have been calculated by assuming a binomial distribution for the number of AEs using SAS.

Table 7-2 Probability of Observing At Least 1 Subject with an AE in the Study if the AE Incidence (θ) is 5% and 10%

Sample Size	θ = 5%	θ = 10%
45	90.0%	99.1%
50	92.3%	99.5%

AE: adverse event

7.3 Randomization

Part A and Part B

Randomization is not relevant (open-label study).

7.4 Blinding and Unblinding

Part A and Part B

This is an open-label study. Refer to Section 10.7 of the CSP for details.

8 ANALYSIS SETS

Part A and Part B

The analysis set will be defined separately for Part A and Part B.

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 analyses.

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 and PD endpoints, unless otherwise specified.

9 STATISTICAL ANALYSIS

9.1 General Considerations

Part A and Part B

Data from Part A and Part B 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.

Note: for subjects who take Orkambi or Symdeko (branded as Symkevi in Europe) during the 28 days before the screening visit, the data collected at screening visit will not be used for baseline derivation for spirometry, sweat chloride and LCI.

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 and Part B 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.

Extended Treatment-emergent (TE) Period for Part B will include the time from the first dose of study drug in Part B through the completion of study participation.

For subjects who do not have unscheduled visit after the Week 24 visit, refer to Section 9.1.6 of the CSP for the definition of completion of study participation. For subjects who have unscheduled visit after the Week 24 visit, the completion of study participation is defined as the date of the last unscheduled visit.

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 periods, and maximum and minimum change from baseline values during TE periods for safety analyses
- In individual subject data listings as appropriate

Visit windowing rules: For analysis specified in Sections 9.2, 9.3, and 9.4, 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 and Part B

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
- Rollover to open-label study (Part B only)

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 and Part B

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 (North America for Part A; North America, Europe [including Australia] for Part B)

Baseline characteristics will include the following:

- CFTR genotype group (F/F, F/MF)
- Weight group (<30 kg, and ≥30 kg)
- Weight (kg)
- Weight z-score
- Height (cm)
- Height z-score
- BMI (kg/m^2)
- BMI z-score

Disease characteristics will include the following:

- $ppFEV_1$ at baseline (<70, ≥70 to ≤90, and >90)
- $ppFEV_1$ at baseline (continuous)
- Sweat chloride at baseline (continuous)

For Part B, the following additional disease characteristics will also be provided:

- CFQ-R respiratory domain score at baseline (child's version; continuous)
- $LCI_{2.5}$ at baseline (continuous)
- Prior use of CFTR modulator (Yes, No)
- 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, the following data listings will also be provided:

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

9.2.3 Medical History

Part A and Part B

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 and Part B

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. For Part B, prior medications will also be summarized the same way as concomitant medications. All medications will be listed for each subject.

9.2.5 Study Drug Exposure

Part A and Part B

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; in weeks for Part B) 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. For Part B, they are specified as: ≤15 days; >15 days and ≤4 weeks; >4 and ≤8 weeks; >8 and ≤12 weeks; >12 and ≤16 weeks; >16 and ≤20 weeks;

>20 and ≤24 weeks; >24 weeks. 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 and patient-years for Part B), will be provided.

9.2.6 Study Drug Compliance

Part A and Part B

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. In addition, for Part B, a study drug interruption that continues through the end of the study participation (i.e., subject does not resume study drug before the end of the study participation) will not be included in the compliance calculation.

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

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 and Part B

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

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. For Part B, besides the listing, a summary table of IPDs based on the FAS will also be provided.

9.3 Efficacy Analysis

9.3.1 Efficacy Summary for Part A

Only summary tables based on the FAS will be provided for efficacy assessments in Part A.

9.3.1.1 Spirometry

For spirometry measurements, a summary of raw values, absolute and relative change from baseline values will be provided at each scheduled time point for the following parameters: FEV_1 (L), forced vital capacity (FVC) (L), FEV_1/FVC (ratio), forced expiratory flow (FEF25%-75%) (L/s), $ppFEV_1$, percent predicted FVC, percent predicted FEF, and percent predicted FEV_1/FVC. The predicted values from spirometry will be calculated using the Global Lung Initiative (GLI) equation. Details on GLI equation are described in Appendix C.

9.3.1.2 Sweat Chloride

The raw values and change from baseline values of sweat chloride measurements will be summarized descriptively (n, mean, SD, median, min, and max) at baseline and post-baseline visits.

9.3.1.3 Weight, Height, BMI and their Z-scores

The raw values and change from baseline values of weight, height, BMI and their z-scores will be summarized descriptively (n, mean, SD, median, min, and max) at baseline and post-baseline visits.

9.3.2 Efficacy Analysis for Part B

There is no multiplicity adjustment; *P*-values provided for the secondary and other endpoints in Part B are considered nominal.

All efficacy analyses described in this section will be based on the FAS, unless otherwise specified. The analysis will include all available measurements through the last scheduled visit, including measurements after treatment discontinuation.

9.3.2.1 Analysis of Primary Efficacy Variables

Not applicable.

9.3.2.2 Analysis of Secondary Efficacy Variables

9.3.2.2.1 Definition of Variables

Percent predicted FEV_1 ($ppFEV_1$): the $ppFEV_1$ value is the ratio of FEV_1 (L) and predicted FEV_1 (L), expressed as a percentage. See Appendix C for more details.

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

Cystic Fibrosis Questionnaire-Revised (CFQ-R): the CFQ-R[1,4,6] is a validated CF-specific instrument that measures quality-of-life domains. This study utilizes two different versions of CFQ-R:

- CFQ-R for Children ages 6 to 11

- CFQ-R for Parents/Caregivers

In both versions, specific questions 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:

$$\text{Scaled score for a domain} = 100 \times (\text{mean (scores of all questions in the domain)} - 1) / 3,$$

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.

Body mass index (BMI): the BMI at each visit is calculated using the weight and height at each visit as follows:

$$\text{BMI} = \text{Weight (kg)} / [\text{Height (m)}]^2$$

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[8], with the age (in months) used for the calculation defined in Appendix A.

Height z-score and Weight z-score: the height z-score and weight z-score, adjusted for age and sex, will be referred to as weight-for-age z-score (weight z-score) and height-for-age z-score (height z-score). The weight z-score and height z-score will be calculated by using Centers for Disease Control and Prevention (CDC) growth charts[8], with the age (in months) used for the calculation defined in Appendix A.

Modified Facial Hedonic Scale: refer to Section 11.3.1 of the CSP for details.

Pulmonary exacerbation (PEx): A PEx is defined as a new or changed antibiotic therapy (intravenous [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 physical examination (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 until the last efficacy assessment, which may be collected up to the Week 24 Visit or the earlier of Day 169 and the end of study participation if the subject does not have the Week 24 Visit.

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

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

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

9.3.2.2.2 Analysis Method

Absolute change in $ppFEV_1$ from baseline through Week 24:

Absolute change from baseline in $ppFEV_1$ will be analyzed using a mixed-effects model for repeated measures (MMRM) approach based on the FAS. The MMRM will be used to estimate the within-group mean absolute change in $ppFEV_1$ through Week 24. The model will include absolute change from baseline in $ppFEV_1$ (including all measurements up to Week 24 [inclusive], both on-treatment measurements and measurements after treatment discontinuation) as the dependent variable, and visit as the fixed effect, with baseline $ppFEV_1$ value and genotype group (F/F vs. F/MF) as covariates. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the *F*-test of 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; consequently, no imputation of missing data will be performed.

The results obtained from the model will be the average treatment effect through Week 24. Note that the Day 15 Visit will not be included in the estimation of the average treatment effect through Week 24 as the treatment effect is not expected to reach the steady state at Day 15. The estimated mean change from baseline in $ppFEV_1$ through Week 24, along with the corresponding 2-sided 95% confidence interval (CI) and *P*-value will be provided. The treatment effect at each post-baseline visit with 95% CI, obtained from the model, will be provided as well.

The analysis will be conducted with the clinic spirometry data only. An additional analysis may also be performed to include pooled spirometry data obtained in clinic and by Air Next Spirometer, if the Air Next Spirometry data are assessed to be reasonably consistent with clinic spirometry data.

[redacted]

[redacted]

Absolute change in sweat chloride from baseline through Week 24:

Analysis of this PD variable will be based on an MMRM similar to the analysis of the absolute change in $ppFEV_1$ from baseline through Week 24 with the baseline sweat chloride included as a covariate instead of baseline $ppFEV_1$. Data obtained from Day 15, Week 4, Week 12, and Week 24 Visits will be included in the model. However, Day 15 Visit will not be included in the estimation of the average treatment effect through Week 24 as the treatment effect is not expected to reach the steady state at Day 15.

Absolute change in the CFQ-R respiratory domain score from baseline through Week 24:

Analysis of this domain (child's version) will be based on an MMRM similar to the analysis of the absolute change in $ppFEV_1$ from baseline through Week 24 with the baseline CFQ-R respiratory domain score (child's version) included as a covariate instead of baseline $ppFEV_1$. Data obtained from Week 4, Week 8, Week 12, Week 16, and Week 24 Visits will be included in the model and all of these visits will be included in the estimation of the average treatment effect through Week 24. The analysis will include only the clinic assessed CFQ-R RD score. An additional analysis may be performed to include CFQ-R RD score assessed at clinic and at home, if the home assessed data are consistent with the clinic assessed data.

Absolute change in BMI and BMI-for-age z-score from baseline at Week 24;

Absolute change in weight and weight-for-age z-score from baseline at Week 24;

Absolute change in height and height-for-age z-score from baseline at Week 24:

Analysis of these variables will be based on an MMRM similar to the analysis of the absolute change in $ppFEV_1$ from baseline through Week 24 with the corresponding baseline included as a covariate instead of baseline $ppFEV_1$. Data obtained from Day 15, Week 4, Week 8, Week 12, Week 16, and Week 24 Visits will be included in the model.

Drug acceptability assessment using Modified Facial Hedonic Scale:

Analysis of this variable will be based on descriptive statistics. The number and percentage (based on the FAS) of subjects in each category will be summarized for each question at all scheduled visit. The analysis will include only the data assessed at clinic. An additional analysis may be performed to include the data assessed at clinic and at home, if the home assessed data are consistent with the clinic assessed data.

Number of PEx and CF-related hospitalizations through Week 24:

The analysis period for these variables will be the same as the PEx analysis period.

PEx will be summarized as described below:

- Number of events:
  - Number of PEx
  - Number of PEx requiring hospitalizations
  - Number of PEx requiring IV antibiotic therapy
  - Number of PEx requiring hospitalization or IV antibiotic therapy
- Duration of events:
  - Number of days with PEx
  - Number of days with PEx requiring hospitalizations
  - Number of days with PEx requiring IV antibiotic therapy
  - Number of days with PEx requiring hospitalization or IV antibiotic therapy

CF-related hospitalizations will be summarized as described below:

- Number of events:
  - Number of planned hospitalizations for CF (i.e., antibiotic therapy)
  - Number of unplanned hospitalizations for reasons other than antibiotic therapy for sinopulmonary signs/symptoms
- Duration of events:
  - Number of days of planned hospitalizations for CF (i.e., antibiotic therapy)
  - Number of days of unplanned hospitalizations for reasons other than antibiotic therapy for sinopulmonary signs/symptoms

For number of events variables, subjects with multiple defined events during the PEx analysis period will be counted multiple times. The annualized duration of events for each subject will be the total number of days with the defined events times 48 weeks divided by the total number of weeks on study up to the end of the PEx analysis period.

Absolute change in $LCI_{2.5}$ from baseline through Week 24:

Analysis of this variable will be based on an MMRM similar to the analysis of the absolute change in $ppFEV_1$ from baseline through Week 24 with the baseline $LCI_{2.5}$ included as a covariate instead of baseline $ppFEV_1$. Data obtained from Day 15, Week 4, Week 12, and Week 24 Visits will be included in the model. However, Day 15 Visit will not be included in the estimation of the average treatment effect through Week 24 as the treatment effect is not expected to reach the steady state at Day 15.

To better assess the longitudinal profile of the efficacy and pharmacodynamics assessments with repeated measures up to Week 24, the LS mean (SE) of the change from baseline at each post-baseline visit along with the 95% CI will be estimated from the corresponding MMRM. The LS mean (SE) at each visit will also be plotted. 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).

9.3.2.2.3 Sensitivity Analysis

Not applicable because the primary endpoints are safety and tolerability assessments.

[redacted]

[redacted]

9.4 Safety Analysis

Part A and Part B

Safety is a secondary objective of Part A, and the primary objective of Part B. All safety analyses will be conducted for Part A and Part B separately, 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 and Part B

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.
- **Extended TEAE: (Part B only)** any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose of study drug in Part B through the end of the Extended Treatment-emergent Period.
- **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 D.

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
- Related serious TEAEs (Part B only)

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.

9.4.2 Clinical Laboratory

Part A and Part B

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 for selected parameters 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 E.

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

Part B Only

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

9.4.3 Electrocardiogram

Part A and Part B

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 for selected parameters during the TE period will be summarized. The threshold analysis criteria are provided in Appendix E.

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

9.4.4 Vital Signs

Part A and Part B

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 for selected parameters during the TE period will be summarized. The threshold analysis criteria are provided in Appendix E.

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

Part B Only

The number and percentage of subjects meeting at least 1 threshold analysis criterion at each visit will be summarized for blood pressure (systolic and diastolic). The threshold analysis criteria are provided in Appendix E.

9.4.5 Pulse Oximetry

Part A and Part B

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 and Part B

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

9.4.7 Physical Examination

Part A and Part B

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

9.4.8 COVID-19 Impacted Visits

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

[redacted]

[redacted]

[redacted]

10 INTERIM AND DMC ANALYSES

10.1 Interim Analysis

Part A

No interim analysis is planned.

Part B

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

10.2 IDMC Analysis

Part A

No IDMC analysis is planned.

Part B

The DMC's objectives and operational details will be defined in a separate document (DMC Charter) which will be finalized before the first subject is screened in Part B of the study. The DMC's planned safety reviews of study data will be outlined in the DMC Charter and DMC Statistical Analysis Plan.

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] Meyer, R. Daniel, et al. Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic. Statistics in Biopharmaceutical Research just accepted (2020): 1-22.

[4] 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.

[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.

[6] 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.

[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 and Efficacy Assessments**

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

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3, 4]
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 Pre-dose and Post-dose Safety Follow-up	1 2 Not applicable Not applicable	≤1 Pre-dose [1, 9] Use nominal visit 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]
Efficacy Assessment and Pharmacodynamic Assessment			
• Spirometry	Day 1 (Baseline) Day 2 Day 8 Day 15 Safety Follow-up	1 2 8 15 Not applicable	≤1 Pre-dose (1, 5] (5, 12] (12, 29] >29
• Sweat Chloride	Day 1 (Baseline) Day 15	1 15	≤1 Pre-dose (1, 29]
• Weight, Height and BMI (and the corresponding z-scores, as applicable)	Day 1 (Baseline) Day 15 Safety Follow-up	1 15 Not applicable	≤1 (1, 29] >29

Table 12-2 Analysis Visit Windows for Safety and Efficacy Assessments in Part B

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3, 4]
Safety Assessment			
• Serum Chemistry	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 12 Week 16 Week 20 Week 24 Safety Follow-up	1 15 29 57 85 113 141 169 Not applicable	≤1 Pre-dose [1, 22] (22, 43] (43, 71] (71, 99] (99, 127] (127, 155] (155, 183] Use nominal visit
• Hematology	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 12 Week 16 Week 24 Safety Follow-up	1 15 29 57 85 113 169 Not applicable	≤1 Pre-dose [1, 22] (22, 43] (43, 71] (71, 99] (99, 141] (141, 183] Use nominal visit
• Vital Signs (excluding weight, height, and BMI)	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 12 Week 16 Week 24 Safety Follow-up	1 15 29 57 85 113 169 Not applicable	≤1 [1, 22] (22, 43] (43, 71] (71, 99] (99, 141] (141, 183] Use nominal visit
• Standard 12-lead ECG	Day 1 (Baseline) Day 15 Week 12 Week 16 Week 24 Safety Follow-up	1 15 85 113 169 Not applicable	≤1 Pre-dose [1, 50] (50, 99] (99, 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 and Pharmacodynamic Assessment			
• Spirometry	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 12 Week 16 Week 24 Safety Follow-up	1 15 29 57 85 113 169 Not applicable	≤1 Pre-dose (1, 22] (22, 43] (43, 71] (71, 99] (99, 141] (141, 183] >183

Table 12-2 Analysis Visit Windows for Safety and Efficacy Assessments in Part B

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3, 4]
• Weight, Height and BMI (and the corresponding z-scores)	Day 1 (Baseline)	1	≤1
	Day 15	15	(1, 22]
	Week 4	29	(22, 43]
	Week 8	57	(43, 71]
	Week 12	85	(71, 99]
	Week 16	113	(99, 141]
	Week 24	169	(141, 183]
	Safety Follow-up	Not applicable	>183
• Modified Facial Hedonic Scale	Day 1	1	≤1
	Day 15	15	(1, 22]
	Week 4	29	(22, 43]
	Week 8	57	(43, 71]
	Week 12	85	(71, 99]
	Week 16	113	(99, 141]
	Week 24	169	(141, 183]
	Safety Follow-up	Not applicable	>183
• CFQ-R	Day 1 (Baseline)	1	≤1
	Week 4	29	(1, 43]
	Week 8	57	(43, 71]
	Week 12	85	(71, 99]
	Week 16	113	(99, 141]
	Week 24	169	(141, 183]
	Safety Follow-up	Not applicable	>183
• Sweat Chloride • Lung Clearance Index	Day 1 (Baseline)	1	≤1 Pre-dose
	Day 15	15	(1, 22]
	Week 4	29	(22, 57]
	Week 12	85	(57, 127]
	Week 24	169	(127, 183]
[redacted]			

Notes:

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

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

[3] For measurements collected on the date of first dose of study drug, if it cannot be determined whether the measurement is before or after the first dose:
a. Scheduled measurement will be treated as pre-dose observation.
b. Unscheduled measurement will be treated as post-dose observation.

[4] For safety assessment, Safety Follow-up analysis visit will be based on nominal Safety Follow-up visit. If a subject doesn't have a nominal Safety Follow-up visit but has an ETT visit with study day >29 for Part A and >183 for Part B, then the ETT visit will be mapped into Safety Follow-up analysis visit.

[5] For efficacy analysis of Part B, if there are assessments with study days > 183, the nominal Safety Follow-up visit will be mapped to the Safety Follow-up visit. If there is only ETT assessment with study day > 183, the ETT visit will be mapped to the Safety Follow-up visit.

Derived Variables:

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

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

   Obtain the informed consent/assent date.

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

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

   Obtain the age at informed consent/assent (in months) in "yy, mm" format (e.g., 24 years, 6 months) from Vital Signs (VS) page at the Screening Visit.

   Obtain the informed consent/assent date.

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

3. Missing first dose date or last dose date

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

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

4. Sweat Chloride:

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

5. Electrocardiogram:

   Baseline will be defined as the most recent non-missing measurement (or the average of triplicate measurements, if the most recent non-missing measurement is obtained in triplicate), before the first dose of study drug in the Treatment Period. 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 (except for Day 15 visit in Part A);
   - For threshold analysis purpose, all reported ECG values will be used.

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

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

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date (in practical, use 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 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 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 D: Imputation Rules for Missing AE Dates

Imputation rules for missing or partial AE start date are defined below. If the imputed AE start date is before the study informed consent/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 E: 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 - ≤20xULN >20xULN	FDA DILI Guidance Jul 2009.
AST	>ULN - ≤3xULN >3x - ≤5xULN >5x - ≤8xULN >8x - ≤20xULN >20xULN	FDA DILI Guidance Jul 2009.
ALT or AST	(ALT>ULN - ≤ 3xULN) or (AST>ULN - ≤3xULN) (ALT>3x - ≤5xULN) or (AST>3x - ≤5xULN) (ALT>5x - ≤8xULN) or (AST>5x - ≤8xULN) (ALT>8x - ≤20xULN) or (AST>8x - ≤20xULN) ALT>20xULN or AST>20xULN	FDA DILI Guidance
Alkaline Phosphatase	>ULN - ≤1.5xULN >1.5x - ≤2.5xULN >2.5x - ≤5xULN >5x - ≤20xULN >20xULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>ULN - ≤1.5xULN >1.5x - ≤2xULN >2x - ≤3xULN >3x - ≤10xULN >10xULN	FDA DILI Guidance Jul 2009.
Direct Bilirubin	>ULN - ≤1.5xULN >1.5x - ≤2xULN >2x - ≤3xULN >3x - ≤10xULN >10xULN	FDA DILI Guidance Jul 2009.
Indirect Bilirubin	>ULN - ≤1.5xULN >1.5x - ≤2xULN >2x - ≤3xULN >3x - ≤10xULN >10xULN	FDA DILI Guidance Jul 2009.

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 >2.5x - ≤5xULN >5x - ≤20xULN >20xULN	CTCAE grade 1-4
Clinical Chemistry (NON-LFT)		
Albumin	<LLN - ≥30 g/L <30 - ≥20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>ULN - ≤1.5xULN >1.5x - ≤2xULN >2x - ≤5xULN >5xULN	Criteria based upon CTCAE
Creatinine	>ULN - ≤1.5xULN >1.5x - ≤3xULN >3x - ≤6xULN >6xULN	CTCAE grades 1-4
Lipase	>ULN - ≤1.5xULN >1.5x - ≤2xULN >2x - ≤5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
Creatine kinase	>ULN - ≤2.5xULN >2.5x - ≤5xULN >5x - ≤10xULN >10xULN	CTCAE grades 1-4
Hematology		
Hemoglobin	Hgb decreased (anemia) <LLN - ≥100 g/L <100 - ≥80 g/L <80 g/L	CTCAE grade 1-3
	Hgb increased >ULN - ≤20 g/L above ULN >20 g/L above ULN - ≤40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3

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

Parameter	Threshold Analysis	Comments
Platelets	Platelet decreased <LLN - ≥75 x 10e9 /L <75 - ≥50 x 10e9 /L <50 - ≥25 x 10e9 /L <25 x 10e9 /L	CTCAE grade 1-4
	Platelet increased >ULN	No CTCAE available
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	>120 mmHg	
	<70 mmHg	
DBP	>80 mmHg	
	<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	