VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX19-445-107, Version 2.0

A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of ELX/TEZ/IVA Combination Therapy in Subjects With Cystic Fibrosis Who Are 6 Years of Age and Older

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2 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
bpm	beats per minute
CF	cystic fibrosis
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, VX-445
FAS	full analysis set
FDC	fixed-dose combination
$FEF_{25-75\%}$	forced expiratory flow, midexpiratory phase
FEV_1	forced expiratory volume in 1 second
FRC	functional residual capacity
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
min	minimum value
MMRM	mixed model repeated measure
N	number of subjects
OLE	open-label extension
PD	pharmacodynamic/pharmacodynamics
PK	pharmacokinetic/pharmacokinetics
$ppFEV_1$	percent predicted FEV_1
PT	preferred term
q12h	every 12 hours

Abbreviation	Term
QRS	Q, R, and S-wave define the QRS-complex in an ECG
QT	QT interval: The duration of ventricular depolarization and subsequent repolarization; it is measured from the beginning of the QRS complex to the end of the T wave
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

3 MODIFICATIONS

3.1 Modifications to the Approved Clinical Study Protocol

Section 12 of the Clinical Study Protocol (CSP, Version 2.0) states that data from Part A and Part B will be analyzed separately. In this SAP Version 3.0, safety data in Part A and Part B data will be pooled together to provide a comprehensive safety analysis for the entire Study 445-107.

3.2 Modifications to the Approved Statistical Analysis Plan

The previous version of the Statistical Analysis Plan (SAP) Version 2.0, dated 28 April 2022, was amended to create the current SAP Version 3.0, dated 13 April 2023. The SAP history is provided below.

SAP history	
Version and Date of SAP	**Comments**
Version 1.0, 18 December 2020.	Original version. Finalized under Clinical Study Protocol (CSP) Version 1.0
Version 2.0, 28 April 2022.	Amendment according to CSP Version 2.0.
Version 3.0, 13 April 2023	Pre-planned amendment to provide analysis details for additional interim and final analysis.

Major modifications since SAP Version 1.0 through SAP Version 3.0 are summarized below.

Change and Rationale	**Affected Sections**
Updated study design according to CSP Version 2.0.	SAP Version 2.0, Section 7.
Editorial changes in Part A (e.g., visit names, end of participations).	SAP Version 2.0, Sections 8, 9.2, 9.3, 10.2, 10.3, 10.4, Appendix A.
Provided analysis details for final analysis	SAP Version 3.0, Sections 8, 9, 10.2.2, 10.3.2, 10.4.2; Appendix A.
Provided analysis details for Week 144 interim analysis	SAP Version 3.0, Section 11.1.2. Appendix A.

3.3 Modifications to the Approved IDMC Charter

Not applicable.

4 INTRODUCTION

This statistical analysis plan (SAP) for Study 445-107 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. 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.

The Vertex Biometrics Department or designee will perform the statistical analysis of the safety and efficacy data; SAS (Version 9.4 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets).

The SAP (Methods) Version 1.0 was finalized and approved prior to data cutoff for the Week 24 Interim Analysis (IA). SAP Version 1.0 specified analysis details for both the Week 24 IA and the final analysis under CSP Version 1.0. After the Week 24 IA, the CSP Version 1.0 was amended to extend the study treatment period from 96 weeks (under CSP Version 1.0) to 192 weeks (under CSP Version 2.0). Accordingly, the SAP Version 1.0 was amended to Version 2.0 to incorporate study design changes in CSP Version 2.0. This SAP Version 3.0 was amended from SAP Version 2.0 to provide analysis details for a planned Week 144 IA (IA will be conducted based on the Part B Week 48 data cutoff. The safety analysis will be based on pooled Part A and Part B data. This IA will hereafter be called Week 144 IA) and the final analysis. This SAP Version 3.0 will be finalized before the data cutoff date of the Week 144 IA. Any revisions to this approved SAP Version 3.0 will be documented and approved in an amendment to this SAP before the data cutoff date of Week 144 IA.

5 STUDY OBJECTIVES

5.1 Primary Objectives

To evaluate the long-term safety and tolerability of ELX/TEZ/IVA in subjects with CF who are 6 years of age and older

5.2 Secondary Objectives

To evaluate the long-term efficacy and pharmacodynamics (PD) of ELX/TEZ/IVA

6 STUDY ENDPOINTS

6.1 Primary Endpoint

Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values,

ECGs, vital signs, pulse oximetry, and ophthalmologic examinations

6.2 Secondary Endpoints

- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$)
- Absolute change in sweat chloride (SwCl)
- Absolute change in CFQ-R respiratory domain (RD) score
- Absolute change in body mass index (BMI) and BMI-for-age z-score
- Number of pulmonary exacerbations (PEx) and CF-related hospitalizations
- Absolute change in lung clearance $index_{2.5}$ ($LCI_{2.5}$)
- Absolute change in weight and weight-for-age z-score
- Absolute change in height and height-for-age z-score

6.3 Exploratory Endpoints

- Absolute change in fecal elastase-1 (FE-1) levels
- Absolute change in serum levels of immunoreactive trypsinogen (IRT)

7 STUDY DESIGN

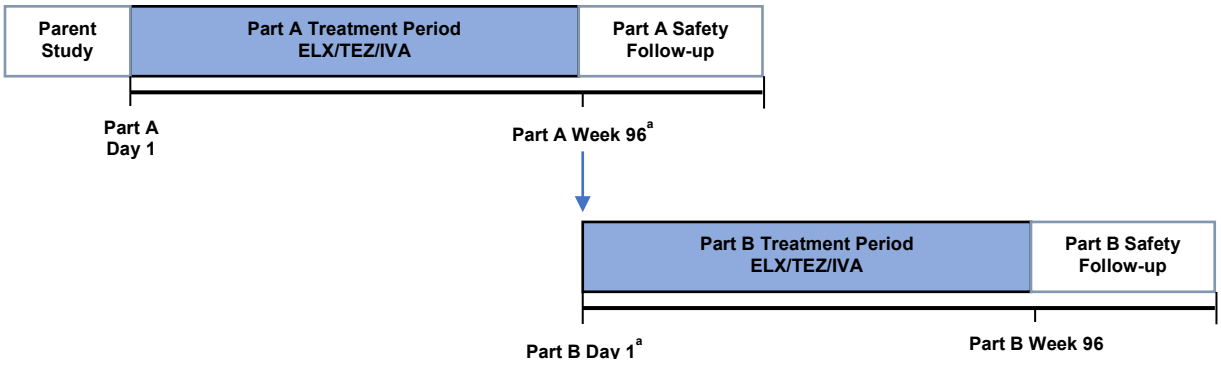
7.1 Overall Design

This is a Phase 3, multicenter, open-label extension study for subjects who completed the Treatment Period in the parent study (VX18-445-106 Part B) and meet eligibility criteria.

A schematic of the study design is shown in Figure 7-1.

Study visits and assessments to be conducted are shown in Table 3-1 and Table 3-2 of the CSP. All visits will occur within the windows specified.

Figure 7-1 Schematic of the Study Design



IVA: ivacaftor; TEZ: tezacaftor
Note: The parent study is VX18-445-106 Part B, a Phase 3 study investigating ELX/TEZ/IVA in subjects 6 through 11 years of age. The figure is not drawn to scale.
[a] Subjects whose Part B Day 1 Visit is on the same day or within 1 calendar day of the Part A Week 96 Visit do NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 96 Visit. Subjects whose Part B Day 1 Visit is more than 1 calendar day after the Part A Week 96 Visit must complete all assessments specified for the Part A Week 96 AND Part B Day 1 Visits.

All subjects will receive ELX/TEZ/IVA at the weight-appropriate dosage levels for 96 weeks in Part A. In Part B, subjects will receive ELX/TEZ/IVA at age- and weight-appropriate dosage levels for 96 weeks (Table 7-1).

Table 7-1 Treatment Period Dosages

Subject Weight	ELX Dosage	TEZ Dosage	IVA Dosage
Part A, subjects ≥6 years of age			
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
<30 kg	100 mg qd	50 mg qd	75 mg q12h
Part B, subjects ≥6 to <12 years of age			
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
<30 kg	100 mg qd	50 mg qd	75 mg q12h
Part B, subjects ≥12 years of age			
All weights	200 mg qd	100 mg qd	150 mg q12h

IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor
Note: Study drug administration is described in Section 9.6.

Part A:

Subjects weighing ≥30 kg at the Part A Day 1 Visit will receive 200 mg ELX once daily (qd)/100 mg TEZ qd/150 mg IVA every 12 hours (q12h) for the duration of the study. Subjects weighing <30 kg at the Part A Day 1 Visit will receive 100 mg ELX qd/50 mg TEZ qd/75 mg IVA q12h. If a subject enters the current study weighing <30 kg and subsequently weighs ≥30 kg at 2 consecutive clinic visits, the dose will be adjusted to the higher dose of 200 mg ELX qd/100 mg TEZ qd/150 mg IVA q12h for the remainder of the study, starting with the second visit where subject's weight is ≥30 kg.

Part B:

In Part B, subjects will receive 200 mg ELX qd/100 mg TEZ qd/150 mg IVA q12h if they meet any of the following criteria:

- Subject is ≥12 years of age
- Subject received 200 mg ELX qd/100 mg TEZ qd/150 mg IVA q12h in Part A
- Subject is ≥30 kg on Part B Day 1

All other subjects <12 years of age and <30 kg will receive 100 mg ELX qd/50 mg TEZ qd/75 mg IVA q12h until either:

- The subject weighs ≥30 kg at 2 consecutive clinic visits in Part B, or
- The subject turns 12 years of age

Once either of the above criteria are met, the subject will receive 200 mg ELX qd/100 mg TEZ qd/150 mg IVA q12h for the remainder of the study.

7.2 Sample Size

The primary and secondary objectives of the study are the evaluation of the long-term safety, tolerability, and efficacy of ELX/TEZ/IVA. This is an open-label study that will enroll subjects who complete study treatment in the parent study and meet eligibility criteria. Sixty-four subjects enrolled in this open-label study.

7.3 Randomization

Randomization is not required because all subjects will be treated identically in a single cohort.

7.4 Blinding and Unblinding

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

8 ANALYSIS SETS

8.1 Analysis Sets for Part A Analysis

8.1.1 All Subjects Set

The **Open-label Extension All Subjects Set** for Part A is defined as all subjects who were enrolled (defined as subject having data in the clinical database) in the corresponding Part. This analysis set will be used for individual subject data listings and disposition summary tables unless otherwise specified.

8.1.2 Safety Set

The **Open-label Extension Safety Set (OLE-SS)** for Part A is defined as all subjects who have received at least 1 dose of study drug in the corresponding Part. The OLE-SS will be used for all safety analyses unless otherwise specified.

8.1.3 Full Analysis Set

The **Study 106 Full Analysis Set (106-FAS)** is defined the same as the FAS definition in the SAP of Study 106 Part B.

The **Open-label Extension Full Analysis Set (OLE-FAS)** for Part A is defined as all enrolled subjects who have received at least 1 dose of study drug in the corresponding Part.

The **Cumulative TC Set** includes subjects who were enrolled and received at least one dose of study drug during the parent study (445-106 Part B) and/or received at least one dose of study drug during the OLE Study.

8.2 Analysis Sets for Final Analysis

8.2.1 All Subjects Set

The **Open-label Extension All Subjects Set** is defined as all subjects who were enrolled (defined as subject having data in the clinical database) in the open-label extension (OLE) study (Study 445-107). This analysis set will be used for individual subject data listings and disposition summary tables in the Week 144 IA and the final analysis unless otherwise specified.

8.2.2 Safety Set

The **Open-label Extension Safety Set (OLE-SS)** is defined as all subjects who have received at least 1 dose of study drug in the OLE study. This analysis set will be used for all safety analyses in the Week 144 IA and the final analysis unless otherwise specified.

8.2.3 Full Analysis Set

The **Study 106 Full Analysis Set (106-FAS)** is defined the same as the FAS definition in the SAP of Study 106 Part B.

The **Open-label Extension Full Analysis Set (OLE-FAS)** is defined as all enrolled subjects who have received at least 1 dose of study drug in the OLE study.

The (**OLE**) **Cumulative TC Set** includes subjects who were enrolled and received at least one dose of study drug during the parent study (445-106 Part B) and/or received at least one dose of study drug during the OLE Study.

9 ANALYSIS PERIOD

The analysis period used for safety and efficacy endpoints in the final analysis is described below.

9.1 Parent Study Efficacy Period

The definition of this analysis period is the same as the PEx analysis period defined in the SAP for Study 445-106 Part B. This analysis period will be used with the parent study efficacy analysis set (106-FAS) to analyze the efficacy data during the parent study.

9.2 Analysis Period for Part A Analysis

OLE Efficacy Period for Part A: Time from the first dose of study drug in the corresponding Part until the last efficacy assessment, which may be collected up to the corresponding Week 96 Visit or the earlier of Day 673 and the end of study participation if subject does not have the corresponding Week 96 Visit in the same Part. This analysis period will be used with the OLE-FAS for the corresponding Part to analyze efficacy data during the corresponding Part.

OLE Safety Period for Part A: Time from the first dose of study drug in the corresponding Part to 28 days after the last dose of the study drug in the corresponding Part or to the completion date of study participation (as defined in Section 9.1.5 of the CSP), whichever occurs first.

The completion date of study participation will be obtained from the end of study page of the eCRF.

The **Treatment-emergent (TE) Period for Part A** is same as the OLE Safety Period for the corresponding Part.

Cumulative TC Efficacy Period for Part A: For subjects who enrolled in Part A, the time from the first dose of study drug in the parent study (445-106 Part B) until the last efficacy assessment in Part A, which may be collected up to the Part A Week 96 Visit or the earlier of Day 673 in Part A and the end of study participation if subject does not have the Part A Week 96 Visit. For subjects who did not enroll in the OLE study and were enrolled and received study drug in the parent study, definition of this analysis period is the same as the parent study efficacy period.

9.3 Analysis Period for Final Analysis

OLE Efficacy Period: Time from the first dose of study drug in the OLE study to the last efficacy assessment, which may be collected up to OLE Part B Week 96 Visit or the earlier of Day 1345 and the end of study participation if subject does not have the OLE Part B Week 96. This analysis period will be used with the OLE-FAS to analyze efficacy data in the Week 144 IA and the final analysis.

OLE Safety Period: Time from the first dose of study drug in the OLE study to 28 days after the last dose of the study drug in the OLE study or to the completion date of study participation (as defined in Section 9.1.5 of the CSP), whichever occurs first.

The completion date of study participation will be obtained from the end of study page of the eCRF.

The **OLE Treatment-emergent (TE) Period** is same as the OLE Safety Period.

The OLE Cumulative TC Efficacy Period: For subjects who enrolled in the OLE study, the time from the first dose of study drug in the parent study (445-106 Part B) until the last efficacy assessment in the OLE study, which may be collected up to the Part B Week 96 Visit or the earlier of Day 1345 and the end of study participation if subject does not have the Part B Week 96 Visit. For subjects who did not enroll in the OLE study and were enrolled and received study drug in the parent study, definition of this analysis period is the same as the parent study efficacy period.

The Cumulative TC Efficacy periods will be used with the Cumulative TC sets for analysis of PEx data.

10 STATISTICAL ANALYSIS

10.1 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, 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 parent study.

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.

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

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

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

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

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

Multiplicity: There will be no multiplicity adjustment as no hypothesis test is planned for safety analysis, unless specified otherwise.

10.2 Background Characteristics

10.2.1 Background Characteristics for Part A

10.2.1.1 Subject Disposition

The number of subjects in the following categories will be summarized based on the Open-label Extension All Subjects Set for Part A:

- Open-label Extension All Subjects Set
- Open-label Extension Safety Set
- Open-label Extension Full Analysis Set
- Never dosed

The number and percentage (based on the OLE-FAS for Part A) 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
- Rolled over to Part B (for Part A only).

Additional disposition categories may be provided for interim analysis, e.g. completed Week 24 Visit and prematurely discontinued treatment before Week 24 Visit and the reason for discontinuation.

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

10.2.1.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized based on the OLE-FAS for Part A.

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, Europe [including Australia])

Baseline characteristics will include the following:

- 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:

- CFTR genotype group (F/F, F/MF)
- $ppFEV_1$ at baseline (<70, ≥70 to ≤90, and >90)
- $ppFEV_1$ at baseline (continuous)
- Sweat chloride at baseline (continuous)
- 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 of the parent study (Positive, Negative)

Prior medication use definition is same as that for the baseline characteristics summary presented in the parent study.

In addition, the following data listings will also be provided:

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

10.2.1.3 Medical History

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

10.2.1.4 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 administered during the 56 days before the first dose of study drug in Part A.
- **Concomitant medication:** medication continued or newly received during the OLE Safety Period for Part A.
- **Post-treatment medication:** medication continued or newly received after the OLE Safety Period for Part A.

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 of Part A, concomitantly during the OLE Safety Period for Part A, or after the OLE Safety Period for Part A, 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 OLE-FAS for Part A using frequency tables by 1) preferred name (PN); and 2) anatomic class (ATC) level 1, ATC level 2, and PN. Prior medications will also be summarized the same way as concomitant medications. All medications will be listed for each subject.

10.2.1.5 Study Drug Exposure

Study drug exposure summaries will be based on the OLE-SS for Part A.

Duration of study drug exposure (in days) will be calculated as [last dose date – first dose date + 1 day] within the OLE Safety Period for Part A, regardless of study drug interruption. For subjects who are still on study drug at IA data cutoff date, the corresponding date will be used as the last dose date for the exposure calculation.

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 into the following categories: <=24 weeks, >24 to <=48 weeks, >48 to <=72 weeks, >72 to <=96 weeks, >96 weeks. 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.

10.2.1.6 Study Drug Compliance

Study drug compliance will be summarized based on the OLE-FAS for Part A.

Study drug compliance will be calculated as: 100 × [1 − (total number of days of study drug interruption started before last dose of study drug) / (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.

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 OLE-FAS for Part A.

10.2.1.7 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.

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

IPDs will be summarized descriptively based on the OLE-FAS for Part A. Additionally, IPDs will be provided in an individual subject data listing.

10.2.2 Background Characteristics for the OLE study

10.2.2.1 Subject Disposition

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

- Open-label Extension All Subjects Set
- Open-label Extension Safety Set
- Open-label Extension Full Analysis Set
- Never dosed

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

- Completed treatment in Part A
- Prematurely discontinued treatment in Part A and the reason for discontinuation
- Completed study in Part A
- Prematurely discontinued the study in Part A and the reason for discontinuation
- Rolled over to Part B

- Completed treatment in Part B
- Prematurely discontinued treatment in Part B and the reason for discontinuation
- Completed study in Part B
- Prematurely discontinued the study in Part B and the reason for discontinuation

Additional disposition categories may be provided for interim analysis (e.g., ongoing at Part B Week 48 Visit, prematurely discontinued treatment before Part B Week 48 Visit and the reason for discontinuation).

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

10.2.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized based on the OLE-FAS. Demographic data will include the following:

- Age at parent study 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, Europe [including Australia])

Baseline characteristics based on parent study will include the following:

- 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 based on parent study will include the following:

- CFTR genotype group (F/F, F/MF)
- $ppFEV_1$ at baseline (<70, ≥70 to ≤90, and >90)
- $ppFEV_1$ at baseline (continuous)
- Sweat chloride at baseline (continuous)
- 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 of the parent study (Positive, Negative)

Prior medication use definition is same as that for the baseline characteristics summary presented in the parent study.

In addition, the following data listings will also be provided:

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

10.2.2.3 Medical History

Medical history will be coded using the MedDRA. For the OLE-FAS, medical history will be summarized descriptively by SOC and PT. The corresponding data listing will also be provided.

10.2.2.4 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 administered during the 56 days before the first dose of study drug in the OLE study.
- **Concomitant medication:** medication continued or newly received during the OLE Safety Period.
- **Post-treatment medication:** medication continued or newly received after the OLE Safety 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 in the OLE study, concomitantly during the OLE Safety Period, or after the OLE Safety 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 OLE-FAS using frequency tables by 1) preferred name (PN); and 2) anatomic class (ATC) level 1, ATC level 2, and PN. Prior medications will also be summarized the same way as concomitant medications. All medications will be listed for each subject.

10.2.2.5 Study Drug Exposure

Study drug exposure summaries will be based on the OLE-SS.

Duration of study drug exposure (in days) will be calculated as [last dose date – first dose date + 1 day] within the OLE Safety Period, regardless of study drug interruption. For subjects who are still on study drug at IA data cutoff date, the corresponding cutoff date will be used as the last dose date for the exposure calculation.

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 into the following categories: <=24 weeks, >24 to <=48 weeks, >48 to <=72 weeks, >72 to <=96 weeks, >96 to <=120 weeks, >120 to <=144 weeks, >144 to <=168 weeks, >168 to <=192 weeks, >192 weeks. 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.

10.2.2.6 Study Drug Compliance

Study drug compliance will be summarized based on the OLE-FAS.

Study drug compliance will be calculated as: 100 × [1 − (total number of days of study drug interruption started before last dose of study drug) / (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.

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 OLE-FAS.

10.2.2.7 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.

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

IPDs will be summarized descriptively based on the OLE-FAS. Additionally, IPDs will be provided in an individual subject data listing.

10.3 Efficacy Analysis

10.3.1 Efficacy Analysis for Part A

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

Continuous endpoints during the parent study will be analyzed using the same mixed-effects model for repeated measures (MMRM) approach as described in the SAP for the parent study. The resulting estimates will be identical to what is available in the final CSR of the parent study. Similarly, continuous endpoints during the OLE efficacy period for part A will be analyzed using a separate MMRM. The results obtained from the parent study and the OLE efficacy period for Part A will be displayed one followed by the other.

There is no multiplicity adjustment.

10.3.1.1 Analysis of Primary Efficacy Variables

Not applicable.

10.3.1.2 Analysis of Secondary Efficacy Variables

10.3.1.2.1 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 13
- 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:

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

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[7], 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[7], with the age (in months) used for the calculation defined in Appendix A.

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 number of PEx is then defined as the total number of PEx during the Cumulative TC Efficacy 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.
- Where 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.

10.3.1.2.2 Analysis Method

Absolute change in ppFEV1 from baseline:

In the MMRM for the OLE efficacy period for Part A, the absolute change from baseline in $ppFEV_1$ will be analyzed using the MMRM approach based on the OLE-FAS for Part A. The model will include absolute change from baseline in $ppFEV_1$ 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 estimated mean change from baseline in $ppFEV_1$ at each post-baseline visit, along with the corresponding 2-sided 95% confidence interval (CI) will be provided.

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.

Absolute change in sweat chloride from baseline:

Analysis of this PD variable will be based on an MMRM similar to the analysis of the absolute change in $ppFEV_1$ from baseline with the baseline sweat chloride included as a covariate instead of baseline $ppFEV_1$.

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

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 with the baseline CFQ-R respiratory domain score (child's version) included as a covariate instead of baseline $ppFEV_1$. The analysis will include clinic assessed CFQ-R RD score only. An additional analysis may be performed to include pooled CFQ-R RD score assessed at clinic and at home, if the home assessed data are reasonably consistent with the clinic assessed data.

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

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

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

Analysis of these variables will be based on an MMRM similar to the analysis of the absolute change in $ppFEV_1$ from baseline with the corresponding baseline included as a covariate instead of baseline $ppFEV_1$. The analysis will be conducted with clinic assessed data only. An additional analysis may be

performed to include data obtained in clinic and at home using the scales and stadiometers provided by Vertex, if the home assessed data are reasonably consistent with the clinic assessed data.

Number of PEx and CF-related hospitalizations:

The analysis of PEx will be based on Cumulative TC Set for Part A, and for the Cumulative TC Efficacy Period for Part A.

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:

Analysis of this variable will be based on an MMRM similar to the analysis of the absolute change in ppFEV1 from baseline with the baseline $LCI_{2.5}$ included as a covariate instead of baseline $ppFEV_1$.

For all continuous endpoints, to better assess the longitudinal profile of the efficacy and pharmacodynamics assessments with repeated measures up to OLE Week 96, the LS means (±SE) for absolute change from baseline 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).

10.3.1.2.3 Sensitivity Analysis

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

10.3.1.2.4 Analysis of Exploratory Efficacy Variables

Absolute change in FE-1 levels from baseline;

Summaries of observed values and change from baseline will be provided by visit. In addition, the number and percentage of subjects with shift changes from baseline (<15 mg/kg, ≥15 mg/kg to <200 mg/kg, and ≥200 mg/kg) at each post-baseline visit (<15 mg/kg, ≥15 mg/kg to <200 mg/kg, and ≥200 mg/kg) will also be provided.

Absolute change in serum levels of IRT from baseline:

Summaries of observed values and change from baseline will be provided by visit. In addition, the number and percentage of subjects with shift changes from baseline (<14ug/L, ≥14ug/L to <40ug/L, and ≥40ug/L) at each post-baseline visit (<14ug/L, ≥14ug/L to <40ug/L, and ≥40ug/L) will also be provided.

10.3.1.2.5 Analysis of Additional Efficacy Variables

Analysis of Additional Spirometry Variables

Summary statistics for raw values and for changes from baseline of the following spirometry measurements will be presented 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 (percentage points)
  - Relative change from baseline in percent predicted FEV_1/FVC (%)

Analysis of Other CFQ-R Variables

Summary statistics for raw values and for changes from baseline of the following CFQ-R domain scores will be presented at each visit.

- CFQ-R respiratory domain score (parent's version)
- CFQ-R non-respiratory domain score (child's version)
- CFQ-R non-respiratory domain score (parent's version)

Analysis of Additional LCI Parameters

Summary statistics for raw values and for changes from baseline of the following LCI parameters will be presented at each visit: $LCI_{2.5}$, $LCI_{5.0}$, and FRC.

10.3.2 Efficacy Analysis for the OLE study

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

Continuous endpoints during the parent study will be analyzed using the same mixed-effects model for repeated measures (MMRM) approach as described in the SAP for the parent study. The resulting estimates will be identical to what is available in the final CSR of the parent study. Similarly, continuous endpoints during the OLE efficacy period will also be analyzed using separate MMRM models for Parts A and B, so that Part A data will be analyzed consistently as what was done in the Part A analysis and the resulting estimates will be identical to the Part A analysis results. The results obtained from the parent study and the OLE efficacy period will be displayed one followed by the other.

There is no multiplicity adjustment.

10.3.2.1 Analysis of Primary Efficacy Variables

Not applicable.

10.3.2.2 Analysis of Secondary Efficacy Variables

10.3.2.2.1 Definition of Variables

The list of variables and their definitions are identical to Section 10.3.1.2.1

10.3.2.2.2 Analysis Method

Absolute change in $ppFEV_1$ from baseline:

For Part A data during the OLE efficacy period, the same model in Section 10.3.1.2.2 will be repeated. For Part B data during the OLE efficacy period, similar MMRM model will be applied based on the OLE-FAS. The model will include absolute change from baseline in $ppFEV_1$ as the dependent variable, and visit in Part B 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 estimated mean change from baseline in $ppFEV_1$ at each post-baseline visit, along with the corresponding 2-sided 95% confidence interval (CI) will be provided.

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.

Absolute change in sweat chloride from baseline:

Analysis of this PD variable will be based on an MMRM similar to the analysis of the absolute change in $ppFEV_1$ from baseline with the baseline sweat chloride included as a covariate instead of baseline $ppFEV_1$.

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

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 with the baseline CFQ-R respiratory domain score (child's version) included as a covariate instead of baseline $ppFEV_1$. The analysis will include clinic assessed CFQ-R RD score only. An additional analysis may be performed to include pooled CFQ-R RD score assessed at clinic and at home, if the home assessed data are reasonably consistent with the clinic assessed data.

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

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

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

Analysis of these variables will be based on an MMRM similar to the analysis of the absolute change in $ppFEV_1$ from baseline with the corresponding baseline included as a covariate instead of baseline $ppFEV_1$. The analysis will be conducted with clinic assessed data only. An additional analysis may be performed to include data obtained in clinic and at home using the scales and stadiometers provided by Vertex, if the home assessed data are reasonably consistent with the clinic assessed data.

Number of PEx and CF-related hospitalizations:

The analysis of PEx will be based on OLE Cumulative TC Set and for the OLE Cumulative TC Efficacy 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 (i.e., OLE Cumulative TC Efficacy 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:

Analysis of this variable will be based on an MMRM similar to the analysis of the absolute change in $ppFEV_1$ from baseline with the baseline $LCI_{2.5}$ included as a covariate instead of baseline $ppFEV_1$.

For all continuous endpoints, to better assess the longitudinal profile of the efficacy and pharmacodynamics assessments with repeated measures up to OLE Part B Week 96, the LS means (±SE) for absolute change from baseline 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).

10.3.2.2.3 Sensitivity Analysis

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

10.3.2.2.4 Analysis of Exploratory Efficacy Variables

Absolute change in FE-1 levels from baseline;

Summaries of observed values and change from baseline will be provided by visit. In addition, the number and percentage of subjects with shift changes from baseline (<15 mg/kg, ≥15 mg/kg to <200 mg/kg, and ≥200 mg/kg) at each post-baseline visit (<15 mg/kg, ≥15 mg/kg to <200 mg/kg, and ≥200 mg/kg) will also be provided.

Absolute change in serum levels of IRT from baseline:

Summaries of observed values and change from baseline will be provided by visit. In addition, the number and percentage of subjects with shift changes from baseline (<14ug/L, ≥14ug/L to <40ug/L, and ≥40ug/L) at each post-baseline visit (<14ug/L, ≥14ug/L to <40ug/L, and ≥40ug/L) will also be provided.

10.3.2.2.5 Analysis of Additional Efficacy Variables

Analysis of Additional Spirometry Variables

Summary statistics for raw values and for changes from baseline of the following spirometry measurements will be presented 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 (percentage points)
  - Relative change from baseline in percent predicted FEV_1/FVC (%)

Analysis of Other CFQ-R Variables

Summary statistics for raw values and for changes from baseline of the following CFQ-R domain scores will be presented at each visit.

- CFQ-R respiratory domain score (parent's version)
- CFQ-R non-respiratory domain score (child's version)
- CFQ-R non-respiratory domain score (parent's version)

Analysis of Additional LCI Parameters

Summary statistics for raw values and for changes from baseline of the following LCI parameters will be presented at each visit: $LCI_{2.5}$, $LCI_{5.0}$, and FRC.

10.4 Safety Analysis

10.4.1 Safety analysis for Part A

All safety analyses will be conducted based on data from the corresponding OLE Safety Period for Part A in the OLE-SS for Part A.

The overall long-term 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

In the AE summary tables, AE data from the OLE Safety Period for Part A may be displayed side-by-side with the AE data from study 445-106 Part B.

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

10.4.1.1 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 in the OLE Safety Period for Part A.
- **TEAE:** any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug through the end of the OLE Safety Period for Part A.
- **Post-treatment AE:** any AE that worsened (either in severity or seriousness) or that was newly developed after the OLE Safety Period for Part A.

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 during OLE Safety Period for Part A 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 frequency counts and percentages as well as the exposure adjusted event rate will be presented for the above overview table. The exposure adjusted rate will not be presented for strongest relationship and maximum severity categories.

The following summary tables of TEAEs during OLE Safety Period 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

Summaries will be presented by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event) and the exposure adjusted event rate (except for summary by strongest relationship and maximum severity). 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 table in which the frequency counts and percentages as well as the exposure adjusted event rate will be presented for TEAEs during the OLE Safety Period for Part A:

- All TEAEs by PT

All AEs in in Part A, including pretreatment AEs, TEAEs, and post-treatment AEs, will be presented in an individual subject data listing based on the OLE All Subjects Set for Part A. 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.

10.4.1.2 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 during the OLE Safety Period for Part A.

The number and percentage of subjects with selected test values meeting at least 1 threshold analysis criterion event during the OLE Safety Period for Part A 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.

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.

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 elevated 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.

10.4.1.3 Electrocardiogram

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

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the OLE Safety Period for Part A 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.

10.4.1.4 Vital Signs

For the vital signs measurements during the OLE Safety Period for Part A, 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 (beats per minute), and respiratory rate (breaths per minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the OLE Safety Period for Part A 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.

10.4.1.5 Pulse Oximetry

For the percent of oxygen saturation measurements using pulse oximetry during the OLE Safety Period for Part A, a summary of observed values and change from baseline values will be provided at each visit.

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 OLE Safety Period for Part A will be summarized. The reference range for normal oxygen saturation is specified as >95%, and <=95% for low oxygen saturation.

10.4.1.6 Ophthalmologic Examinations

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

10.4.1.7 Physical Examination

No tables/figures/listings will be provided for PE data.

10.4.1.8 COVID-19 Impacted Visits

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

10.4.1.9 Supportive Safety Analysis

10.4.1.9.1 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:

- 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 (with the first dose date of study drug in Part A as the reference while calculating time-to-onset)

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

- Sex (male, female)

10.4.2 Safety analysis for the OLE study

All safety analyses will be conducted based on the OLE Safety Period for subjects in the OLE-SS.

The overall long-term 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

In the AE summary tables, AE data from the OLE Safety Period may be displayed side-by-side with the AE data from the parent study 445-106 Part B.

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

10.4.2.1 Adverse Events

For analysis purpose, 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 OLE Safety Period.
- **TEAE:** any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug through the end of the OLE Safety Period.
- **Post-treatment AE:** any AE that worsened (either in severity or seriousness) or that was newly developed after the OLE Safety Period.

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 during OLE Safety Period 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 frequency counts and percentages as well as the exposure adjusted event rate will be presented for the above overview table. The exposure adjusted rate will not be presented for strongest relationship and maximum severity categories.

The following summary tables of TEAEs during OLE Safety Period 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

Summaries will be presented by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event) and the exposure adjusted event rate (except for summary by strongest relationship and maximum severity). 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 table in which the frequency counts and percentages as well as the exposure adjusted event rate will be presented for TEAEs during the OLE Safety Period:

- 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 OLE 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.

10.4.2.2 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 during the OLE Safety Period.

The number and percentage of subjects with selected test values meeting at least 1 threshold analysis criterion event during the OLE Safety 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.

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.

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 elevated 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.

10.4.2.3 Electrocardiogram

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

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the OLE Safety 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.

10.4.2.4 Vital Signs

For the vital signs measurements during the OLE Safety Period, 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 (beats per minute), and respiratory rate (breaths per minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the OLE Safety 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.

10.4.2.5 Pulse Oximetry

For the percent of oxygen saturation measurements using pulse oximetry during the OLE Safety Period, a summary of observed values and change from baseline values will be provided at each visit.

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 OLE Safety Period will be summarized. The reference range for normal oxygen saturation is specified as >95%, and <=95% for low oxygen saturation.

10.4.2.6 Ophthalmologic Examinations

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

10.4.2.7 Physical Examination

No tables/figures/listings will be provided for PE data.

10.4.2.8 COVID-19 Impacted Visits

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

10.4.2.9 Supportive Safety Analysis

10.4.2.9.1 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:

- 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 (with the first dose date of study drug in the OLE study as the reference while calculating time-to-onset)

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

- Sex (male, female)

11 INTERIM AND DMC ANALYSES

11.1 Interim Analysis

In the protocol it has been mentioned that IA may take place at any time during the study at the discretion of the sponsor to support regulatory and/or reimbursement dossiers. An interim analysis was conducted when the last subject reached Part A Week 24. The analysis details of the Week 24 interim analysis were provided in Section 11.1.1 below. Another IA will be conducted when the last subject reaches Part B Week 48, i.e., Week 144 in the OLE study. The analysis details of the Week 144 IA are provided in Section 11.1.2. Unless specified otherwise, the general rules, principles, and scopes specified in Section 10 apply to the IAs.

11.1.1 Week 24 Interim Analysis

For the following efficacy endpoints, the model-based main analysis was performed using the models specified in Section 10.3.1.2.2 with the Extended OLE Week 24 Visit windowing rule defined in Appendix F. Additional analyses was performed using the exact same model but with the regular Week 24 visit windowing rule defined in Appendix A. The descriptive summary for continuous efficacy endpoints also used the Extended OLE Week 24 Visit windowing rule.

- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$)
- Absolute change in sweat chloride (SwCl)
- Absolute change in CFQ-R respiratory domain (RD) score
- Absolute change in body mass index (BMI) and BMI-for-age z-score
- Absolute change in lung clearance $index_{2.5}$ ($LCI_{2.5}$)
- Absolute change in weight and weight-for-age z-score
- Absolute change in height and height-for-age z-score

The descriptive summary tables for continuous safety endpoints stayed with the regular OLE Week 24 Visit windowing rule defined in Appendix A and were restricted to the last visit at which the number of subjects was at least 10.

11.1.2 Week 144 Interim Analysis

The following efficacy endpoints will be analyzed using methods specified in Section 10.3.2.2.2. Both MMRM models and descriptive summaries will include data up to the OLE Part B Week 48 (inclusive) analysis visit. The windowing rules are provided in Appendix B.

- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$)
- Absolute change in sweat chloride (SwCl)
- Absolute change in CFQ-R respiratory domain (RD) score
- Absolute change in body mass index (BMI) and BMI-for-age z-score
- Absolute change in lung clearance $index_{2.5}$ ($LCI_{2.5}$)

- Absolute change in weight and weight-for-age z-score
- Absolute change in height and height-for-age z-score
- Pulmonary Exacerbation (PEx) and CF-related hospitalizations

The study is conducted during the COVID-19 pandemic. If extra assessments (e.g., unscheduled visits) will be collected to mitigate the impact of COVID-19 pandemic on this Week 144 IA, Extended OLE Part B Week 48 analysis visit may replace the regular OLE Part B Week 48 analysis visit for efficacy analysis, using the exact same analysis methods. In such situations, MMRM models with the regular OLE Part B Week 48 analysis visit may be conducted as additional analysis. All efficacy analysis for the Week 144 IA will be based on clinical assessed data.

The same definition on analysis period as described in Section 9 applies to this IA but the analysis period does not exceed the IA data cutoff date. The descriptive summary tables for continuous safety endpoints will stay with the regular visit windowing rule defined in Appendix A and will be restricted to the last visit at which the number of subjects is at least 10. For AE, PEx, similar event base parameters, all available data will be included.

11.2 IDMC Analysis

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

12 REFERENCES

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[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.

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13 LIST OF APPENDICES

- **Appendix A: Analysis Visit Windows for Safety and Efficacy Assessments**

Table 13-1Analysis Visit Windows for Safety and Efficacy Assessments for Part A

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2]
Safety Assessment			
Serum Chemistry Hematology Vital Signs (excluding Weight, Height, BMI, and corresponding z-scores)[3]	Baseline OLE Part A Week 8 OLE Part A Week 16 OLE Part A Week 24 OLE Part A Week 36 OLE Part A Week 48 OLE Part A Week 60 OLE Part A Week 72 OLE Part A Week 84 OLE Part A Week 96 Safety Follow-up[4]	1 57 113 169 253 337 421 505 589 673 Not applicable	defined in section 8.1 [1, 85] (85, 141] (141, 211] (211, 295] (295, 379] (379, 463] (463, 547] (547, 631] (631, 687] Use nominal visit
Standard 12-lead ECG Coagulation	Baseline OLE Part A Week 24 OLE Part A Week 48 OLE Part A Week 72 OLE Part A Week 96 Safety Follow-up[4]	1 169 337 505 673 Not applicable	defined in section 8.1 [1, 253] (253, 421] (421, 589] (589, 687] Use nominal visit
Efficacy Assessment			
Spirometry Weight, Height and BMI (and the corresponding z-scores)	Baseline OLE Part A Week 8 OLE Part A Week 16 OLE Part A Week 24 OLE Part A Week 36 OLE Part A Week 48 OLE Part A Week 60 OLE Part A Week 72 OLE Part A Week 84 OLE Part A Week 96 Safety Follow-up[5]	1 57 113 169 253 337 421 505 589 673 Not applicable	defined in section 8.1 (1, 85] (85, 141] (141, 211] (211, 295] (295, 379] (379, 463] (463, 547] (547, 631] (631, 687] >687

Table 13-1Analysis Visit Windows for Safety and Efficacy Assessments for Part A			
Assessment	**Visit[1]**	**Target Study Day**	**Analysis Visit Window (in study days)[2]**
CFQ-R	Baseline	1	defined in section 8.1
	OLE Part A Week 8	57	(1, 113]
	OLE Part A Week 24	169	(113, 253]
	OLE Part A Week 48	337	(253, 421]
	OLE Part A Week 72	505	(421, 589]
	OLE Part A Week 96	673	(589, 687]
	Safety Follow-up[5]	Not applicable	>687
Sweat chloride Lung Clearance Index IRT	Baseline	1	defined in section 8.1
	OLE Part A Week 24	169	(1, 253]
	OLE Part A Week 48	337	(253, 421]
	OLE Part A Week 72	505	(421, 589]
	OLE Part A Week 96	673	(589, 687]
FE-1	Baseline	1	defined in section 8.1
	OLE Part A Week 24	169	(1, 211]
	OLE Part A Week 48	337	(211, 505]
	OLE Part A Week 96	673	(505, 687]

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 measurement collected on the date of first dose of study drug in Treatment Period, if it cannot be determined whether the measurement is before or after the first dose:

1. Scheduled measurement will be treated as pre-dose observation.
2. 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 >687, then the ETT visit will be mapped into Safety Follow-up analysis visit.

[5] For efficacy assessment, if a subject has nominal safety follow up visit with study day >687, then nominal Safety Follow-up visit will be mapped to Safety Follow-up visit; else if subject doesn't have a nominal safety follow-up visit with study day > 687 but has an ETT visit with study day >687, then the ETT visit will be mapped into Safety Follow-up analysis visit; else if there are multiple assessments with >687 then select the earliest record.

Derived Variables:

Table 13-1Analysis Visit Windows for Safety and Efficacy Assessments for Part A			
Assessment	**Visit[1]**	**Target Study Day**	**Analysis Visit Window (in study days)[2]**
1.Age (in years) at first dose date and post-baseline visit (for demographics, listing and the calculation of [percent] predicted spirometry variables): Obtain the age at informed consent in "yy, mm" format (e.g., 24 years, 6 months) in parent study from the Vital Signs (VS) page at the Screening Visit in parent study and add 0.5 month to convert to days. Obtain the informed consent date in parent study. Then age (in years) at first dose or post-baseline visit = [(first dose date or post-baseline visit date – informed consent date in parent study) in days + age at informed consent (in days) in parent study]/365.25. 2.Age (in months) at first dose date and post-baseline visit (for use in calculation of BMI): Obtain the age at informed consent in "yy, mm" format (e.g., 24 years, 6 months) in parent study from the VS page at the Screening Visit in the parent study. Obtain the informed consent date in parent study. Then age (in months) at first dose or post-baseline visit = integer part of {[(age at informed consent (in months) in parent study + 0.5 + diff(first dose date or post-baseline visit date, informed consent date) in months in parent study]} + 0.5. 3.Missing first dose date or last dose date If the first dose date is missing, use Day 1 visit date. If the last dose date of study drug is not available and there is no data to indicate that the subject discontinued treatment, the data cutoff date will be used instead. If the subject discontinued treatment and 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 data cutoff date. 4.Electrocardiogram: Baseline is defined in Section 8.1. If multiple ECG measurements are obtained on the same calendar day during the TE period, ○For summary purpose, the average value will be used as the ECG on that day; ○For threshold analysis purpose, all ECG values will be used			

Table 13-2 Analysis Visit Windows for Safety and Efficacy Assessments for the OLE study			
Assessment	**Visit[1]**	**Target Study Day**	**Analysis Visit Window (in study days)[2]**
Safety Assessment			
Serum Chemistry Hematology Vital Signs (excluding Weight, Height, BMI, and corresponding z-scores)[3]	Baseline	1	defined in section 8.1
	OLE Part A Week 8	57	[1, 85]
	OLE Part A Week 16	113	(85, 141]
	OLE Part A Week 24	169	(141, 211]
	OLE Part A Week 36	253	(211, 295]
	OLE Part A Week 48	337	(295, 379]
	OLE Part A Week 60	421	(379, 463]
	OLE Part A Week 72	505	(463, 547]
	OLE Part A Week 84	589	(547, 631]
	OLE Part A Week 96	673	(631, 715]
	OLE Part B Week 12	757	(715, 799]
	OLE Part B Week 24	841	(799, 883]
	OLE Part B Week 36	925	(883, 967]
	OLE Part B Week 48	1009	(967, 1051]
	OLE Part B Week 60	1093	(1051, 1135]
	OLE Part B Week 72	1177	(1135, 1219]
	OLE Part B Week 84	1261	(1219, 1303]
	OLE Part B Week 96	1345	(1303, 1359]
	Safety Follow-up[4]	Not applicable	Use nominal visit
Standard 12-lead ECG Coagulation	Baseline	1	defined in section 8.1
	OLE Part A Week 24	169	[1, 253]
	OLE Part A Week 48	337	(253, 421]
	OLE Part A Week 72	505	(421, 589]
	OLE Part A Week 96	673	(589, 757]
	OLE Part B Week 24	841	(757, 925]
	OLE Part B Week 48	1009	(925, 1093]
	OLE Part B Week 72	1177	(1093, 1261]
	OLE Part B Week 96	1345	(1261, 1359]
	Safety Follow-up[4]	Not applicable	Use nominal visit
Efficacy Assessment[5]			
Part A: same as in Table 13-1			
Part B: see below			

Table 13-2 Analysis Visit Windows for Safety and Efficacy Assessments for the OLE study			
Assessment	**Visit[1]**	**Target Study Day**	**Analysis Visit Window (in study days)[2]**
Spirometry Weight, Height and BMI (and the corresponding z-scores)	Baseline	1	defined in section 8.1
	OLE Part B Week 12	757	(667, 799]
	OLE Part B Week 24	841	(799, 883]
	OLE Part B Week 36	925	(883, 967]
	OLE Part B Week 48	1009	(967, 1051]
	OLE Part B Week 60	1093	(1051, 1135]
	OLE Part B Week 72	1177	(1135, 1219]
	OLE Part B Week 84	1261	(1219, 1303]
	OLE Part B Week 96	1345	(1303, 1401]
	Safety Follow-up[6]	Not applicable	>1401
CFQ-R	Baseline	1	defined in section 8.1
	OLE Part B Week 24	841	(667, 925]
	OLE Part B Week 48	1009	(925, 1093]
	OLE Part B Week 72	1177	(1093, 1261]
	OLE Part B Week 96	1345	(1261, 1401]
	Safety Follow-up[6]	Not applicable	>1401
Sweat chloride Lung Clearance Index IRT	Baseline	1	defined in section 8.1
	OLE Part B Week 24	841	(667, 925]
	OLE Part B Week 48	1009	(925, 1093]
	OLE Part B Week 72	1177	(1093, 1261]
	OLE Part B Week 96	1345	(1261, 1401]
FE-1	Baseline	1	defined in section 8.1
	OLE Part B Week 48	1009	(667, 1177]
	OLE Part B Week 96	1345	(1177, 1401]

Notes:

[1,2,3]: See **Table 13-1**.

[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 a Part A ETT visit with study day >687 or a Part B ETT visit with study day >1359, then the ETT visit will be mapped into Safety Follow-up analysis visit.

[5] For efficacy windowing rules, Part A data will only be used to derive Part A analysis visits using the window rules in **Table 13-1**. Part B data will only be used to derive Part B analysis visits using the window rules in this table. Note that Safety Follow-up visits from both Parts will be combined for efficacy summary tables.

[6] For efficacy assessment in Part B, if a subject has nominal Part B safety follow up visit with study day >1359, then nominal Safety Follow-up visit will be mapped to Safety Follow-up visit; else if subject doesn't have a nominal safety follow-up visit with study day >1359 but has an ETT visit with study day >1359, then the ETT visit will be mapped into Safety Follow-up analysis visit; else if there are multiple assessments with >1401 then select the earliest record.

Derived Variables: See **Table 13-1**.

Table 13-3 Efficacy Analysis Visit Windows for Week 144 Interim Analysis if Extended OLE Part B Week 48 is used.

Assessment	Visit	Target Study Day	Analysis Visit Window (in study days)
Efficacy Assessment			
Part A: same as in Table 13-1			
Part B: see below			
Spirometry Weight, Height and BMI (and the corresponding z-scores)	Baseline OLE Part B Week 12 OLE Part B Week 24 OLE Part B Week 36 Extended OLE Part B Week 48	1 757 841 925 1009	defined in section 8.1 (667, 799] (799, 883] (883, 967] >967
CFQ-R	Baseline OLE Part B Week 24 Extended OLE Part B Week 48	1 841 1009	defined in section 8.1 (667, 925] >925
Sweat chloride Lung Clearance Index	Baseline OLE Part B Week 24 Extended OLE Part B Week 48	1 841 1009	defined in section 8.1 (667, 925] >925

Notes: The above analysis windows will be used only when mitigation plans regarding the impact of COVID-19 pandemic will be implemented. See Section 11.1.2 for details.

See **Table 13-1** table notes for detailed.

▪ 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 13-4 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: https://www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools/it-engineers-and-manufacturers/ [Accessed Sep 22, 2020].

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: https://www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools/it-engineers-and-manufacturers/ [Accessed Sep 22, 2020].

Sanja Stanojevic. GLI-2012 - SAS Macro (Version 2, 7 April 2013). Global Lung Function Initiative. [online] Available at: https://www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools/sas-macro/ [Accessed Sep 22, 2020].

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. Ongoing events of the parent study will follow the imputation rule described in the SAP of parent study.

- **If only Day of AE start date is missing:**
    - If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then
        - if AE start year and month are equal to the month and year of first dose date, then impute the AE start day as the day of first dose date;
        - 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 or AE end date is missing, then
        - if AE start year is equal to the year of first dose date, then impute the AE start month and day as the month and day of first dose date;
        - 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.
    - else impute the AE start date as the informed consent date.

Imputation rules for partial AE end date are defined below:

If partial end date, then impute as min (the last day of the month, data cut-off, end of study) if day is missing, or min (Dec, data cut-off, end of study) if month is missing.

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

Table 13-5 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Clinical Chemistry (LFT)		
ALT	>ULN to ≤3xULN >3x to ≤5xULN >5x to ≤8xULN >8x to ≤20xULN >20xULN	FDA DILI Guidance Jul 2009.
AST	>ULN to ≤3xULN >3x to ≤5xULN >5x to ≤8xULN >8x to ≤20xULN >20xULN	FDA DILI Guidance Jul 2009.
ALT or AST	(ALT>ULN to ≤ 3xULN) or (AST>ULN to ≤3xULN) (ALT>3x to ≤5xULN) or (AST>3x to ≤5xULN) (ALT>5x to ≤8xULN) or (AST>5x to ≤8xULN) (ALT>8x to ≤20xULN) or (AST>8x to ≤20xULN) ALT>20xULN or AST>20xULN	FDA DILI Guidance
Alkaline Phosphatase	>ULN to ≤1.5xULN >1.5x to ≤2.5xULN >2.5x to ≤5xULN >5x to ≤20xULN >20xULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>ULN to ≤1.5xULN >1.5x to ≤2xULN >2x to ≤3xULN >3x to ≤10xULN >10xULN	FDA DILI Guidance Jul 2009.
Direct Bilirubin	>ULN to ≤1.5xULN >1.5x to ≤2xULN >2x to ≤3xULN >3x to ≤10xULN >10xULN	FDA DILI Guidance Jul 2009.
Indirect Bilirubin	>ULN to ≤1.5xULN >1.5x to ≤2xULN >2x to ≤3xULN >3x to ≤10xULN >10xULN	FDA DILI Guidance Jul 2009.

Table 13-5 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 to ≤2.5xULN >2.5x to ≤5xULN >5x to ≤20xULN >20xULN	CTCAE grade 1-4
Clinical Chemistry (NON-LFT)		
Albumin	<LLN to ≥30 g/L <30 to ≥20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>ULN to ≤1.5xULN >1.5x to ≤2xULN >2x to ≤5xULN >5xULN	Criteria based upon CTCAE
Creatinine	>ULN to ≤1.5xULN >1.5x to ≤3xULN >3x to ≤6xULN >6xULN	CTCAE grades 1-4
Lipase	>ULN to ≤1.5xULN >1.5x to ≤2xULN >2x to ≤5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
Creatine kinase	>ULN to ≤2.5xULN >2.5x to ≤5xULN >5x to ≤10xULN >10xULN	CTCAE grades 1-4
Hematology		
Hemoglobin	Hgb decreased (anemia) <LLN to ≥100 g/L <100 to ≥80 g/L <80 g/L	CTCAE grade 1-3
	Hgb increased >ULN to ≤20 g/L above ULN >20 g/L above ULN to ≤40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3

Table 13-5 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Platelets	Platelet decreased <LLN to ≥75 x 10e9 /L <75 to ≥50 x 10e9 /L <50 to ≥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 to ≤1.5xULN >1.5 to ≤2.5xULN >2.5xULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN to ≤1.5xULN >1.5 to ≤2.5xULN >2.5 x ULN	CTCAE grade 1-3

Table 13-6 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 13-7 Threshold Analysis Criteria for Vital Signs

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

Table 13-7 Threshold Analysis Criteria for Vital Signs

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

▪ Appendix F: Analysis Visit Windows for Efficacy Assessments at Week 24 Interim Analysis

Table 13-8 Analysis Visit Windows for Efficacy Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2]
Efficacy Assessment			
Spirometry Weight, Height and BMI (and the corresponding z-scores)	Baseline OLE Week 8 OLE Week 16 Extended OLE Week 24	1 57 113 169	defined in section 8.1 (1, 85] (85, 141] >141
CFQ-R	Baseline OLE Week 8 Extended OLE Week 24	1 57 169	defined in section 8.1 (1, 113] >113
Sweat chloride Lung Clearance Index	Baseline Extended OLE Week 24	1 169	defined in section 8.1 >1

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.