VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX22-445-122, Version 4.0

A Phase 3, Open-label Study Evaluating the Pharmacokinetics, Safety, and Tolerability of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 12 to Less Than 24 Months of Age

[redacted]

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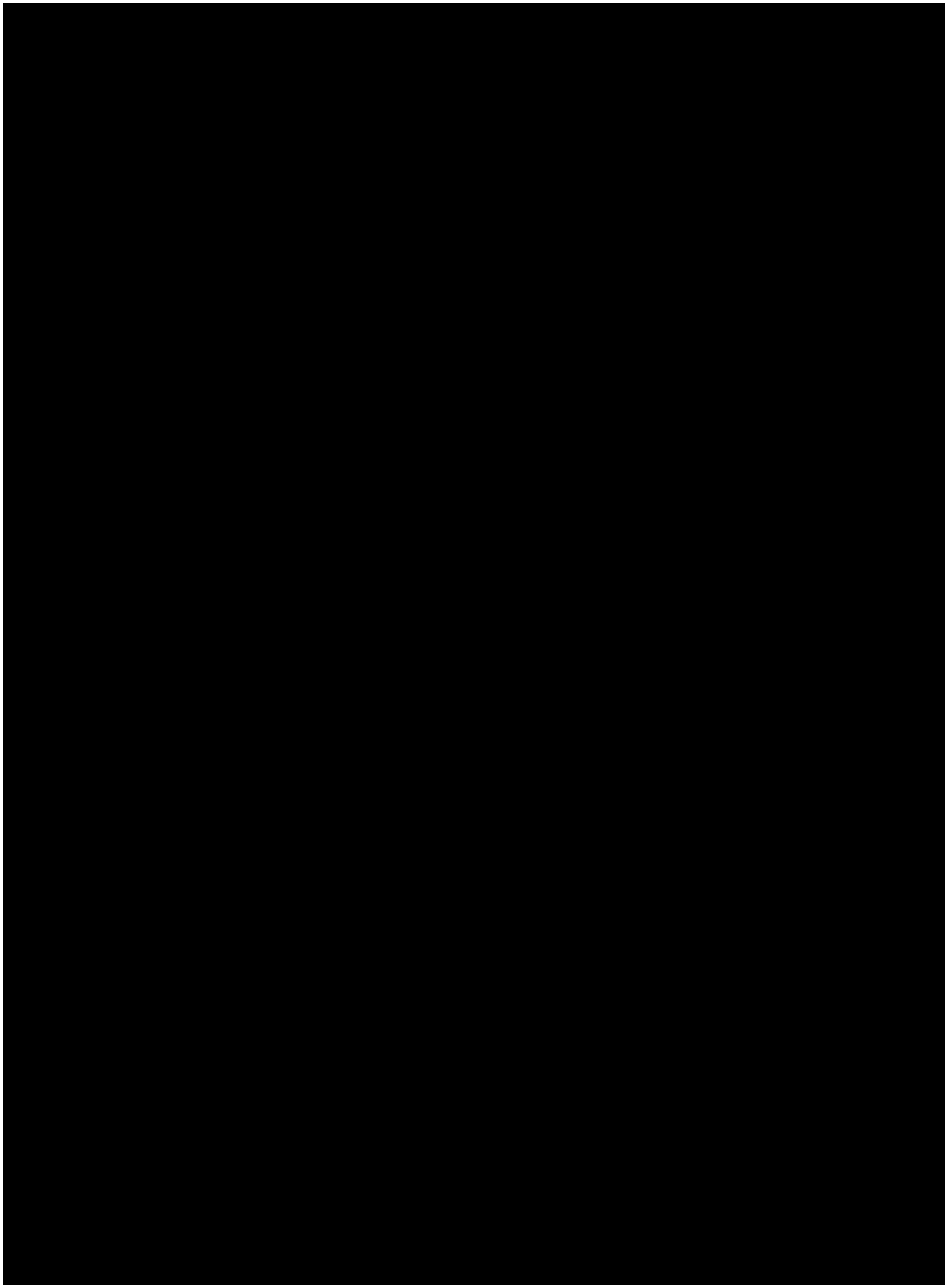
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2 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
[redacted]	
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical class
BMI	body mass index
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator protein or the gene encoding the protein
CI	confidence interval
CSP	clinical study protocol
ECG	electrocardiogram
eCRF	electronic case report form
ELX	elexacaftor
FAS	full analysis set
FE-1	fecal elastase
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
IDMC	independent data monitoring committee
IRT	immunoreactive trypsinogen
IV	intravenous
IVA	ivacaftor
LCI	lung clearance index
LFT	liver function test
LS means	Least Squares means
max	maximum value
MBW	multiple breath washout
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum value
MMRM	mixed effects model for repeated measures
N	number of subjects
OLE	open-label extension
PD	pharmacodynamic(s)
PEx	pulmonary exacerbations
PK	pharmacokinetic(s)
PN	Preferred Name
PT	Preferred Term
qAM	once every morning
qPM	once every evening
QRS	Q, R, and S-wave define the QRS-complex in an ECG

Abbreviation	Term
QT	QT interval
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
SwCl	sweat chloride
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary



4 INTRODUCTION

Study VX22-445-122 (Study 445-122) is a Phase 3, open-label, 2-part (Parts A and B), multicenter study evaluating the pharmacokinetics (PK), safety, tolerability, pharmacodynamics (PD), and efficacy of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) in cystic fibrosis (CF) subjects 12 to <24 months of age with at least one *F508del* mutation in the *CFTR* gene or another ELX/TEZ/IVA-responsive *CFTR* mutation.

This statistical analysis plan (SAP) Version 2.0 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.

The previous SAP (Version 1.0, 31 October 2023) documented the planned statistical analyses of safety and tolerability data for Part A and was finalized and approved prior to the data lock for Part A. This SAP (Version 2.0) is a preplanned amendment to provide analysis of the safety and efficacy data for Part B. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP.

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

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).

5 STUDY OBJECTIVES

5.1 Primary Objectives

Part A

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

Part B

To evaluate the safety and tolerability of ELX/TEZ/IVA

5.2 Secondary Objectives

Part A

None

Part B

- To evaluate the PK of ELX, TEZ, IVA, and relevant metabolites
- To evaluate the PD of ELX/TEZ/IVA
- To evaluate the efficacy of ELX/TEZ/IVA

6 STUDY ENDPOINTS

6.1 Primary Endpoints

Part A

- PK parameters of ELX, TEZ, IVA, and relevant metabolites
- Safety and tolerability assessments as determined by adverse events (AEs), clinical laboratory values, standard 12-lead electrocardiograms (ECGs), vital signs, and pulse oximetry

Part B

Safety and tolerability assessments as determined by AEs, clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry

6.2 Secondary Endpoints

Part A

None

Part B

- PK parameters of ELX, TEZ, IVA, and relevant metabolites
- Absolute change in sweat chloride (SwCl) from baseline through Week 24

6.3 Other Endpoints

Part A

None

Part B

- Number of pulmonary exacerbations (PEx) and CF-related hospitalizations through Week 24
- Absolute change in weight and weight-for-age z-score from baseline at Week 24
- Absolute change in length and length-for-age z-score from baseline at Week 24
- Absolute change in body mass index (BMI) and BMI-for-age z-score from baseline at Week 24
- Absolute change in weight-for-length z-score from baseline at Week 24
- Absolute change in fecal elastase-1 (FE-1) levels from baseline at Week 24
- Absolute change in serum levels of immunoreactive trypsinogen (IRT) from baseline at Week 24
- Absolute change in fecal calprotectin levels from baseline at Week 24
- Absolute change in lung clearance index $(LCI)_{2.5}$ from baseline through Week 24

- Acceptability and palatability of ELX/TEZ/IVA granules at Day 1 and at Week 24

7 STUDY DESIGN

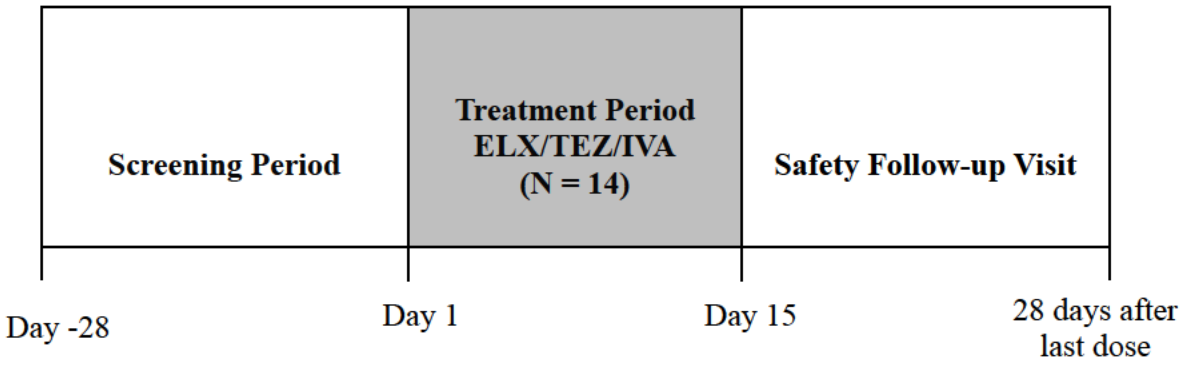
7.1 Overall Design

This is a Phase 3, open-label, 2-part (Parts A and B), multicenter study evaluating the PK, safety, tolerability, PD, and efficacy of ELX/TEZ/IVA in CF subjects 12 to <24 months of age.

Part A

A schematic of the study design for Part A is provided in **Figure 7-1**. Approximately 14 subjects will be enrolled in Part A. During the Treatment Period, subjects will be administered ELX/TEZ/IVA for approximately 15 days (**Table 7-1**). Safety, tolerability, and available PK data will be reviewed by Vertex after Part A to confirm or revise the dosage levels chosen for Part B. Based on emerging PK data, additional subjects may be enrolled as needed in Part A in order to provide sufficient information to select the dose(s) for Part B.

Figure 7-1 VX22-445-122 Part A Study Design



ELX: elexacaftor; IVA: ivacaftor; N: total sample size; TEZ: tezacaftor
Note: ELX/TEZ/IVA will be administered from Day 1 through Day 15. The last dose of study drug will be the morning dose (ELX/TEZ/IVA) at the Day 15 Visit; the evening dose (IVA) will not be administered that day.

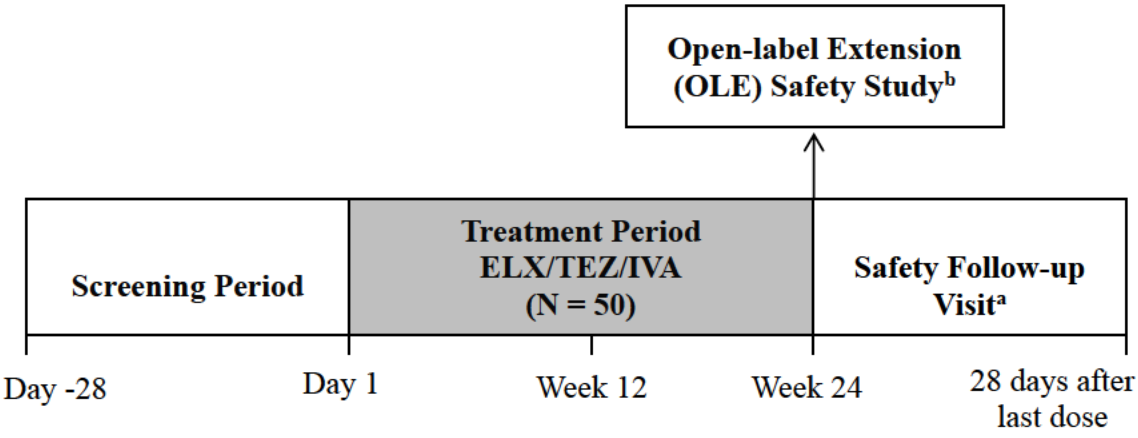
Part B

A schematic of the study design for Part B is provided in **Figure 7-2**. Part B will initiate after available data from Part A have been reviewed by Vertex and the Part B dose(s) has been confirmed or adjusted. Part B will enroll approximately 50 subjects, of whom at least 15 subjects will have F/MF genotypes and at least 15 subjects will have the F/F genotype. Subjects will be enrolled sequentially in Cohort B1 (18 to <24 months of age) followed by Cohort B2 (12 to <18 months of age). Initiation of Cohort B2 will be based on a review by Vertex of all Cohort B1 PK data through Week 4 and all safety data through Week 8. During the Treatment Period, subjects will be administered ELX/TEZ/IVA for approximately 24 weeks (**Table 7-1**).

An optional LCI Substudy will be conducted.

Subjects from Cohorts B1 and B2 who are eligible will be offered the opportunity to enroll in an open-label extension (OLE) safety study.

Figure 7-2 VX22-445-122 Part B Study Design



ELX: elexacaftor; IVA: ivacaftor; N: total sample size; OLE: open-label extension; TEZ: tezacaftor

[a] The Safety Follow-up Visit is not required for subjects who enroll in an OLE safety study within 28 days of the last scheduled visit in the Treatment Period.

[b] Subjects who are eligible will be offered the opportunity to enroll in an OLE safety study evaluating ELX/TEZ/IVA.

Table 7-1 VX22-445-122 Dose Regimens (Parts A and B)

Subject Weight at Day 1	ELX Dose	TEZ Dose	IVA Dose
Part A			
[redacted]kg only	40 mg qAM	20 mg qAM	30 mg qAM 25 mg qPM
Part B			
[redacted] kg	80 mg qAM	40 mg qAM	60 mg qAM 59.5 mg qPM
[redacted] kg to [redacted] kg	60 mg qAM	30 mg qAM	45 mg qAM 50 mg qPM
[redacted]kg	40 mg qAM	20 mg qAM	30 mg qAM 25 mg qPM

ELX: elexacaftor; IVA: ivacaftor; qAM: once every morning; qPM: once every evening; TEZ: tezacaftor

7.2 Sample Size and Power

Part A

Approximately 14 subjects will be enrolled in Part A. Sample size calculations were determined based on ELX and M23-ELX estimates of clearance. Assuming that the variability in this age group is the same as the variability observed in adults, data from 14 subjects will allow at least 80% power to target a 95% confidence interval (CI) within 60% and 140% of the geometric mean estimate of clearance for ELX and M23-ELX.

Part B

No formal power calculation was performed. The number of subjects in Part B is deemed adequate to meet the primary safety objective. Approximately 50 subjects will be enrolled. The incidence of AEs is a safety endpoint. With 40 subjects expected to complete Part B, there is a >95% chance of observing an AE in at least 1 subject if the true incidence rate is 10%. **Table 7-2** presents estimated probabilities for observing at least 1 subject with an AE for the given incidence rate (θ) and number of subjects completing Part B. The probabilities were calculated by assuming a binomial distribution for the number of AEs using SAS®.

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

Number of Subjects Completing Part B	θ = 5%	θ = 10%
40	87.1%	98.5%
45	90.1%	99.1%

θ: incidence; AE: adverse event

7.3 Randomization

Not needed. Both Part A and Part B are designed to be single arm and open-label.

7.4 Blinding and Unblinding

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

8 ANALYSIS SETS

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

8.1 All Subjects Set

The **All Subjects Set** will include all subjects who are enrolled (defined as subjects having data in the clinical database) or received at least 1 dose of study drug. This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

8.2 Full Analysis Set (Part B only)

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

8.3 Safety Set

The **Safety Set** will include all subjects who receive at least 1 dose of study drug. The Safety Set will be used for all safety analyses, unless otherwise specified.

8.4 LCI Substudy Set (Part B only)

The **LCI Substudy Set** will include all subjects in the FAS who signed informed consent to the optional LCI Substudy. LCI-related tables and figures will be based on the LCI Substudy Set.

9 STATISTICAL ANALYSIS

9.1 General Considerations

Data from Part A and Part B will be analyzed separately.

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

Continuous variables will be summarized using the following descriptive summary statistics: 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.

Treatment-emergent (TE) Period for Parts A and B will include the time from the first dose of study drug in the respective Part to 28 days after the last dose of study drug, or to the completion of study participation date in the respective Part (as defined in Section 9.1.6 of the CSP), whichever occurs first.

Baseline value, unless specified otherwise, will be defined for Parts A and B as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the respective Part.

Note: In Part B, for subjects who take CFTR modulators (e.g., Orkambi) during the 28 days before the screening visit(s), the data collected less than 28 days from the date of last CFTRm use will not be used for baseline derivation for SwCl and LCI. In addition, historical values will not be considered for baseline derivation.

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

Visit windowing rules for protocol-defined visits are provided in Appendix A: Analysis Visit Windows for Safety and Efficacy Assessments.

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

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

9.2 Background Characteristics

9.2.1 Background Characteristics for Part A

9.2.1.1 Subject Disposition

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

- All Subjects Set
- Safety Set

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

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

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

9.2.1.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized based on the Safety Set.

Demographic data will include the following:

- Age at Day 1 (months)
- Sex (male; female)
- Ethnicity (Hispanic or Latino; Not Hispanic or Latino; Not Collected per Local Regulations)
- Race (White; Black or African American; Asian; American Indian or Alaska Native; Native Hawaiian or Other Pacific Islander; Other; Not Collected per Local Regulations)

Baseline characteristics will include the following:

- CFTR genotype group (F/F; F/MF; other)
- Weight (kg)
- Length (cm)
- BMI (kg/m^2)
- Weight-for-length

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

- Informed consent
- Inclusion/exclusion criteria violations for subjects with any such violations

9.2.1.3 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For the Safety Set, medical history will be summarized descriptively by System Organ Class (SOC) and Preferred Term (PT). The corresponding data listing will also be provided.

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

9.2.1.4 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 was administered during the 56 days before the TE Period
- **Concomitant medication:** medication continued or newly received during the TE Period
- **Post-treatment medication:** medication continued or newly received after the TE Period

A given medication may be classified as follows: prior, concomitant, post-treatment, both prior and concomitant, both concomitant and post-treatment, or prior, concomitant, and post-treatment.

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

Concomitant medications will be summarized descriptively based on the Safety Set using frequency tables by: 1) Preferred Name (PN); and by 2) Anatomical Therapeutic Chemical class (ATC) level 1, ATC level 2, and PN. All medications will be listed for each subject.

9.2.1.5 Study Drug Exposure

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

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

Study drug exposure (in days) will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized by interval using counts and percentages: ≤2 days; >2 days to ≤4 days; >4 to ≤8 days; >8 to ≤15 days; >15 days. Additionally, the total study drug exposure, defined as the sum total of the study drug exposure across all subjects (in patient-weeks), will be provided.

9.2.1.6 Study Drug Compliance

Study drug compliance will be summarized based on the Safety Set.

Study drug compliance will be calculated as: 100 × [1 – (total number of days of study drug interruption) / (duration of study drug exposure in days)]. A study drug interruption on a given day is defined as an interruption of any study drug dose or component on that day.

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%.

9.2.1.7 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that may significantly impact the completeness, accuracy, and/or reliability of key 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.

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

9.2.2 Background Characteristics for Part B

9.2.2.1 Subject Disposition

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

- All Subjects Set
- Full Analysis Set (FAS)
- Safety Set
- Enrolled but not dosed
- LCI Substudy Set

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

- Completed treatment

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

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

9.2.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the FAS.

Demographic data will include the following:

- Age at Day 1 (months)
- Age group at Day 1 (12 to <18 months; 18 to <24 months)
- Sex (male; female)
- Ethnicity (Hispanic or Latino; Not Hispanic or Latino; Not Collected per Local Regulations)
- Race (White; Black or African American; Asian; American Indian or Alaska Native; Native Hawaiian or Other Pacific Islander; Other; Not Collected per Local Regulations)
- Geographic region (North America; Europe [including Australia])

Baseline characteristics will include the following:

- CFTR genotype group (F/F; F/MF; Other)
- Weight group at Day 1 (<7 kg; ≥7 to <10 kg; ≥10 kg)
- Weight (kg); Weight z-score
- Length (cm); Length z-score
- BMI (kg/m^2); BMI z-score
- Weight-for-length percentile; Weight-for-length z-score

Disease characteristics will include the following:

- Sweat chloride at baseline (continuous)
- Prior use of CFTR modulator (Yes; No)
- Prior use of dornase alpha (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* prior to screening (Positive; Negative)

Similar tables for demographics and baseline characteristics will be provided based on the LCI Substudy Set.

In addition, the following data listings will be provided:

- Informed consent
- Inclusion/exclusion criteria violations for subjects with any such violations

9.2.2.3 Medical History

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

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

9.2.2.4 Prior and Concomitant Medications

Medications will be coded using WHODrug and classified as prior, concomitant, or post-treatment, as defined in 9.2.1.4.

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 study drug, concomitantly during the TE Period, or after the TE Period, it will be classified as prior, concomitant, and post-treatment. Details for imputing missing or partial start and/or stop dates of medication are described in Appendix B.

Prior and concomitant medications will be summarized descriptively for the FAS using frequency tables by: 1) PN; and by 2) ATC level 1, ATC level 2, and PN. All medications will be listed for each subject.

9.2.2.5 Study Drug Exposure

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

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

Study drug exposure (in weeks) will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized by interval using counts and percentages. The categories are specified as: ≤15 days; >15 days to ≤4 weeks; >4 to ≤8

weeks; >8 to ≤12 weeks; >12 to ≤16 weeks; >16 to ≤20 weeks; >20 to ≤24 weeks; >24 weeks. Additionally, the total study drug exposure, defined as the sum total of the study drug exposure across all subjects (in patient-weeks and patient-years), will be provided.

9.2.2.6 Study Drug Compliance

Study drug compliance will be summarized based on the FAS.

Study drug compliance will be calculated as: 100 × [1 – (total number of days of study drug interruption) / (duration of study drug exposure in days)]. A study drug interruption on a given day is defined as an interruption of any study drug dose or component on that day. A study drug interruption that continues through the end of study participation (i.e., subject does not resume study drug before the end of study participation) will not be included in the compliance calculation.

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

9.2.2.7 Important Protocol Deviations

IPD is defined in 9.2.1.7. IPDs will be provided in an individual subject data listing. Additionally, a summary table of IPDs based on the FAS will be provided.

9.3 Efficacy Analysis

9.3.1 Efficacy Analysis for Part A

Not applicable. There is no efficacy endpoint in Part A.

9.3.2 Efficacy Analysis for Part B

All efficacy analyses described in this section will be based on the FAS, unless otherwise specified. LCI-related analysis will be based on the LCI Substudy Set. Analyses will include all available measurements through the last visit, including measurements after treatment discontinuation.

There is no multiplicity adjustment; *P* values provided for secondary and other endpoints are considered nominal.

9.3.2.1 Analysis of Primary Efficacy Variables

Not applicable as efficacy is not a primary endpoint.

9.3.2.2 Analysis of Secondary Efficacy Variables

9.3.2.2.1 Definition of Variables

Sweat chloride: The SwCl value at a given visit will be calculated as the mean of the non-missing SwCl 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 SwCl. Any results reported as having volume <15 µL or SwCl values reported as <10 mmol/L or >160 mmol/L will be considered missing.

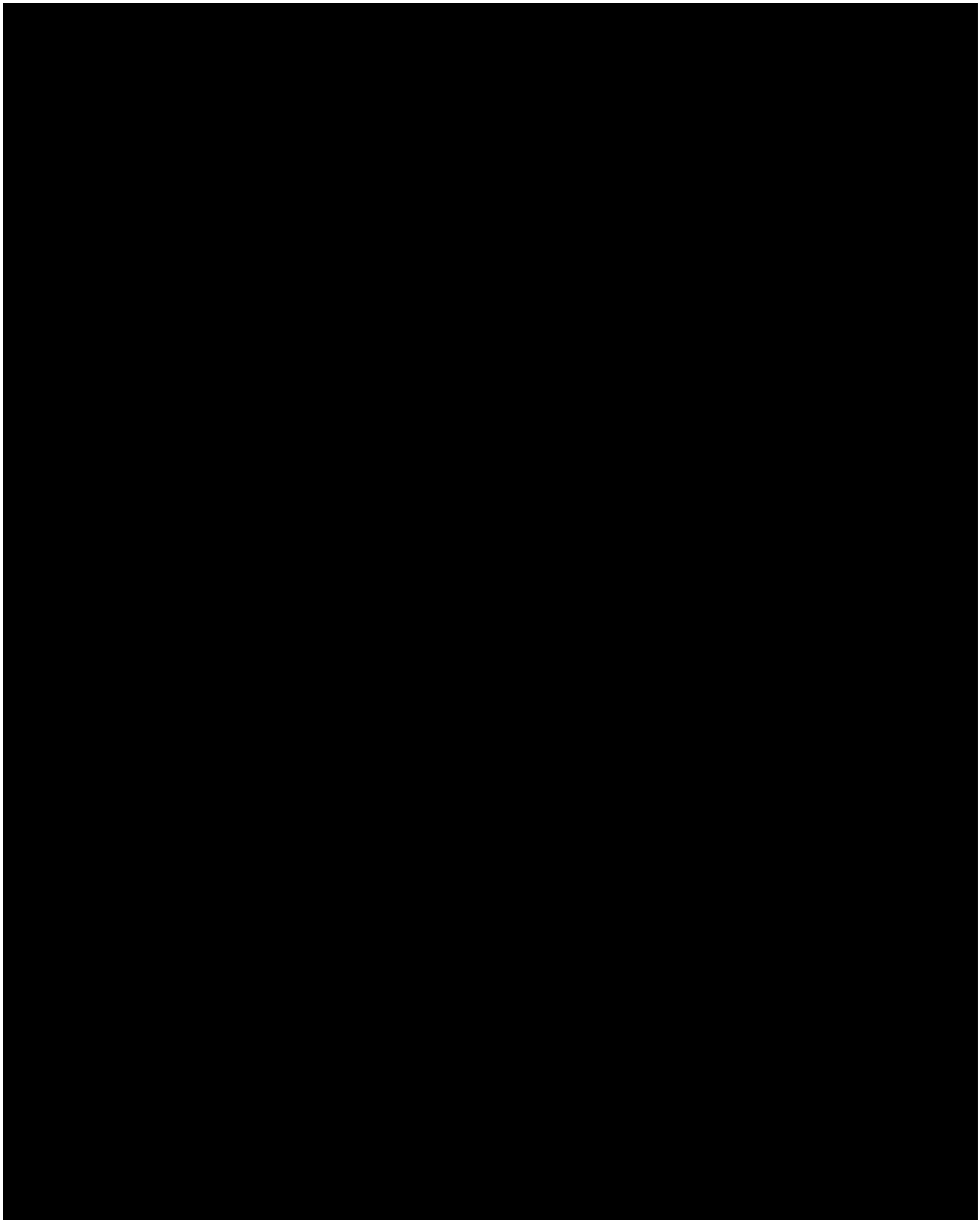
9.3.2.2.2 Analysis Method

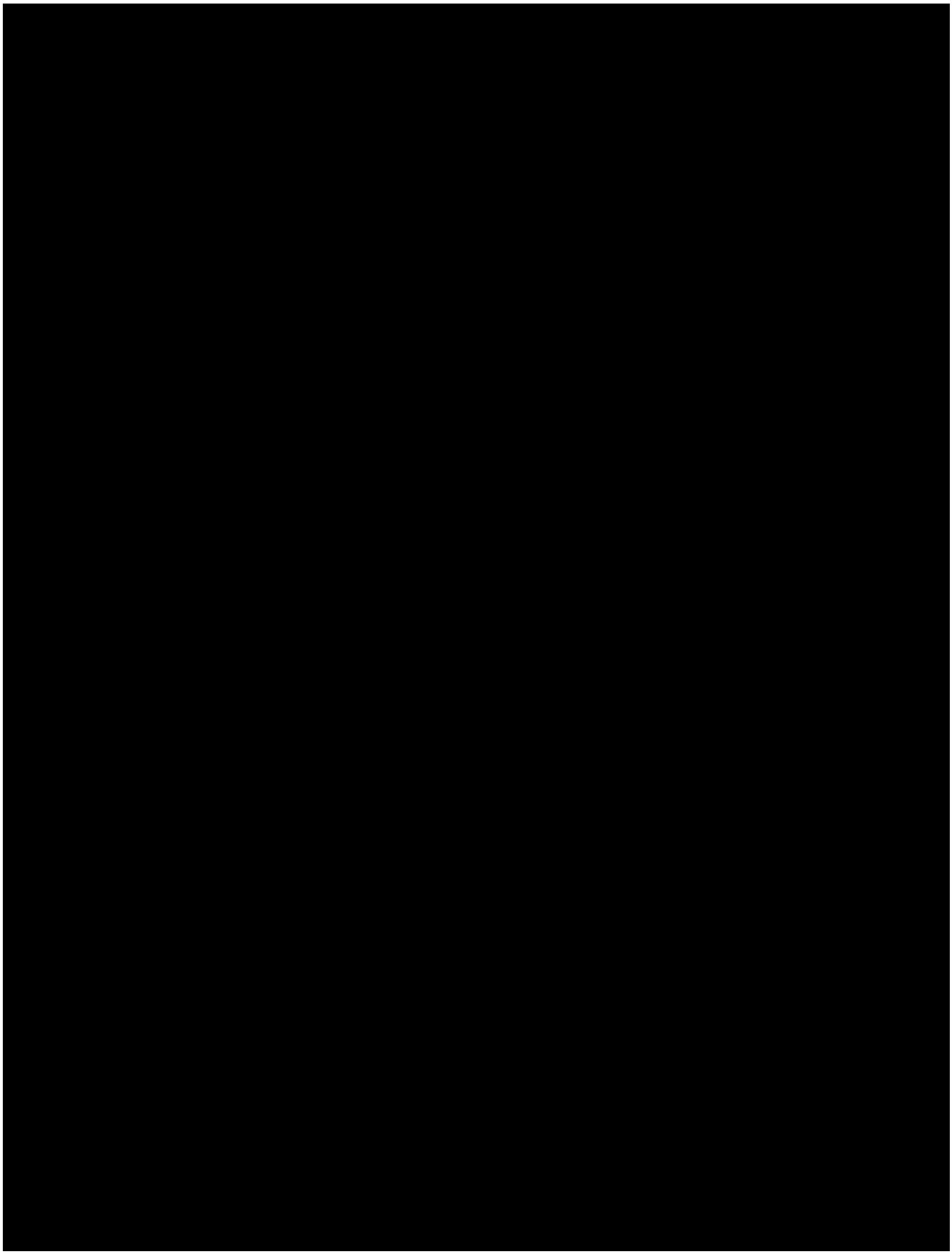
Absolute change in SwCl from baseline through Week 24:

Absolute change from baseline in SwCl will be analyzed using a mixed-effects model for repeated measures (MMRM) approach based on the FAS. The MMRM will be used to estimate the within-group mean absolute change in SwCl through Week 24. The model will include absolute change from baseline in SwCl (including all measurements up to and including Week 24) as the dependent variable, with visit, baseline SwCl value, and genotype group (F/F, F/MF, other) as covariates. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the *F*-test for fixed effects will be estimated using the Kenward-Roger approximation[1]. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, an alternative covariance structure like compound symmetry may be used. If the model still does not converge, genotype may be collapsed into F/F and other, or removed from the model. Conditional on the observed data and covariates, missing data will be assumed to be missing at random.

The primary result obtained from the model will be the average treatment effect through Week 24, estimated using all post-baseline visits up to and including Week 24. The estimated mean change from baseline in SwCl through Week 24 along with the corresponding 2-sided 95% CI and *P* value will be provided. The treatment effect at each post-baseline visit obtained from the model will also be provided, and the LS mean (standard error, SE) at each visit will be plotted. In addition, the post-baseline raw values and the absolute change from baseline at each post-baseline visit will be summarized.







[redacted]

9.3.2.4 Sensitivity Analysis

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

[redacted]

[redacted]

9.4 Safety Analysis for Part A and Part B

Safety is a primary objective. All safety analyses described below will be presented for Part A and Part B separately, unless specified otherwise. Safety analysis will be based on data from the TE Period using the Safety Set.

The following safety and tolerability endpoints will be assessed:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry

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

9.4.1.1 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 corresponding Part
- **TEAE:** any AE that worsened (either in severity or seriousness) or that was newly developed on or after the first dose of study drug through the end of the TE Period in the corresponding Part
- **Post-treatment AE:** any AE that worsened (either in severity or seriousness) or that was newly developed after the TE Period in the corresponding Part

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

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

An overview of all TEAEs will be provided with the following categories:

- Number of TEAEs (total number of TEAEs only)
- Subjects with any TEAEs

- Subjects with TEAEs by strongest relationship
- Subjects with TEAEs by maximum severity
- Subjects with TEAEs leading to study drug discontinuation (discontinuation of any study drug)
- Subjects with TEAEs leading to study drug interruption (interruption of any study drug)
- Subjects with Grade 3/4/5 TEAEs
- Subjects with related TEAEs
- Subjects with serious TEAEs
- Subjects with related serious TEAEs
- Subjects with TEAEs leading to death

The following summary tables of TEAEs will be presented:

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- Related TEAEs
- TEAEs leading to study drug discontinuation (discontinuation of any study drug)
- TEAEs leading to study drug interruption (interruption of any study drug)
- Grade 3/4/5 TEAEs
- Serious TEAEs
- Related serious TEAEs
- TEAEs leading to death

Summaries will be presented by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, 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 in the relationship summaries.

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

- All TEAEs by PT
- Related TEAEs by PT

All AEs, including pretreatment AEs, TEAEs, and post-treatment AEs, will be presented in an individual subject data listing based on the All Subjects Set. In addition, separate listings containing individual subject AE data for TEAEs leading to study drug discontinuation, TEAEs leading to study drug interruption, Grade 3/4/5 TEAEs, all serious AEs (SAEs), and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.

9.4.1.2 Clinical Laboratory

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

For select laboratory parameters, the number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE Period will be summarized. The threshold analysis criterion shift from baseline will also be summarized for select laboratory parameters. The threshold analysis criteria are provided in Appendix D.

A listing containing individual subject hematology, chemistry, and coagulation values will be provided. Listings will include data from both scheduled and unscheduled visits.

The following additional analyses will be performed for Part B only:

- For select LFT laboratory tests (ALT, AST, ALP, and total bilirubin), a scatterplot of the maximum TE value versus the baseline value corresponding to ×ULN will be presented. Furthermore, a scatterplot of the maximum TE value of ALT and AST, separately, versus the maximum TE value of total bilirubin corresponding to ×ULN will also be presented.
- A listing of subjects who meet the criteria of [(ALT>3×ULN or AST>3×ULN) and TBILI>2×ULN] at any visit will be provided and will present values for ALT, AST, ALP, and total bilirubin.

9.4.1.3 Electrocardiogram

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

The number and percentage of subjects meeting at least 1 threshold analysis criterion for select parameters during the TE Period will be summarized. The threshold analysis criteria are provided in Appendix D.

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

9.4.1.4 Vital Signs

For treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized at each visit for the following vital signs parameters: [redacted] systolic and diastolic blood

pressure (mmHg), body temperature (°C), pulse rate (beats/minute), and respiratory rate (breaths/minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion for select parameters during the TE Period will be summarized. The threshold analysis criteria are provided in Appendix D. Additionally, for Part B, the number and percentage of subjects meeting threshold analysis criteria at each visit will be summarized for blood pressure (systolic and diastolic).

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

9.4.1.5 Pulse Oximetry

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

The number and percentage of subjects with shift change from baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the TE Period will be summarized. The reference range for normal oxygen saturation is specified as >95%, and as ≤95% for low oxygen saturation.

9.4.1.6 Ophthalmologic Examinations

Ophthalmologic examination results will be presented in individual subject data listings.

9.4.1.7 Physical Examination

Abnormal physical examination findings will be reported as AEs.

9.4.1.8 Visit Type

A listing containing the impact of the COVID-19 pandemic on subjects' visits or information on subjects with non-clinic visits will be provided, as applicable to each Part.



[redacted]

10 INTERIM AND IDMC ANALYSES

10.1 Interim Analysis

Part A and Part B

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

10.2 IDMC Analysis

Part A and Part B

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

11 REFERENCES

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

[2]Schumacher, D. (2020). anthro: Computation of the WHO Child Growth Standards. R package version 0.9.4. Retrieved from: https://cran.r-project.org/web/packages/anthro/anthro.pdf

[3]World Health Organization. (2006). WHO Child Growth Standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Retrieved from: https://www.who.int/publications/i/item/924154693X

12 LIST OF APPENDICES

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

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

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3, 4]
• Serum Chemistry • Standard 12-lead ECG • Vital Signs and Pulse Oximetry	Day 1 (Baseline) Day 8 Day 15 Safety Follow-up	1 8 15 Not applicable	≤1 Pre-dose (1, 12] (12, 29] Use nominal visit
• Hematology	Baseline Day 15 Safety Follow-up	1 15 Not applicable	≤1 Pre-dose (1, 29] Use nominal visit
• Weight, height (length), and BMI[5]	Day 1 (Baseline) Day 15 Safety Follow-up	1 15 Not applicable	≤1 (1, 29] >29

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

• Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3, 4]
Safety Assessments			
• Serum Chemistry • Hematology (not collected on Day 1) • Vital Signs and Pulse Oximetry	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 12 Week 16 Week 20 Week 24 Safety Follow-up	1 15 29 57 85 113 141 169 Not applicable	≤1 Pre-dose [1, 22] (22, 43] (43, 71] (71, 99] (99, 127] (127, 155] (155, 183] Use nominal visit
• Standard 12-lead ECG	Day 1 (Baseline) Day 15 Week 12 Week 24 Safety Follow-up	1 15 85 169 Not applicable	≤1 Pre-dose [1, 50] (50, 127] (127, 183] Use nominal visit
• Coagulation	Baseline Week 20	Not applicable 141	≤1 Pre-dose [1, 183]
Efficacy Assessments[5]			
• Sweat chloride	Day 1 (Baseline) Week 4 Week 12 Week 24	1 29 85 169	≤1 Pre-dose (1, 57] (57, 127] (127, 183]

• Weight, height (length), and BMI (and corresponding z-scores)	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 12 Week 16 Week 20 Week 24 Safety Follow-up	1 15 29 57 85 113 141 169 Not applicable	≤1 Pre-dose (1, 22] (22, 43] (43, 71] (71, 99] (99, 127] (127, 155] (155, 183] >183
• Lung Clearance Index	Day 1 (Baseline) Week 12 Week 24	1 85 169	≤1 Pre-dose (1, 127] (127, 183]
• FE-1 • Fecal Calprotectin	Day 1 (Baseline) Day 15 Week 4 Week 12 Week 24	1 15 29 85 169	≤1 Pre-dose (1, 22] (22, 57] (57, 127] (127, 183]
• IRT	Baseline Day 15 Week 8 Week 12 Week 24	Not applicable 15 57 85 169	≤1 Pre-dose (1, 36] (36, 71] (71, 127] (127, 183]
• Acceptability Palatability Assessment	Day 1 (Baseline) Week 24	1 169	≤1 Pre-dose (1, 183]

Notes:

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

[2] 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, and there are both scheduled and unscheduled visits, then the unscheduled visit will be selected.

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

[4] For safety assessments, the Safety Follow-up (SFU) analysis visit will be based on the nominal SFU visit. If a subject does not have a nominal SFU visit but has an early termination of treatment (ETT) visit with study day >29 in Part A or >183 in Part B, then the ETT visit will be mapped to the SFU analysis visit.

[5] For weight, height (length), BMI, and weight-for-length in Part A, and for efficacy assessments in Part B, if a subject has a nominal SFU visit with study day >29 in Part A or >183 in Part B, the nominal SFU visit will be mapped to the SFU analysis visit; else if a subject does not have a nominal SFU visit with study day >29 in Part A or >183 in Part B but has an ETT visit with study day >29 in Part A or >183 in Part B, then the ETT visit will be mapped to the SFU analysis visit; else if a subject has a nominal Day 15 visit or unscheduled visit in Part A with study day >29 prior to the end of study date, or a nominal Week 24 visit or unscheduled visit in Part B with study day >183 prior to the end of study date, then this visit will be mapped to the Day 15 analysis visit in Part A or the Week 24 analysis visit in Part B.

Derived Variables:

1. If full date of birth is not available, age at first dose date and nominal visits is derived as the following:

- Obtain the age at informed consent (IC, in days) from the Vital Signs (VS) page at the Screening Visit:

  Age at IC (in days) = Age at IC (in years)*365.25 + Age at IC (in months)*40.3375 + 15.22

- Obtain the informed consent date.
- Age (in years) at first dose or nominal visit = [(first dose date or nominal visit date – informed consent date + age at IC (in days)]/365.25 (for blood pressure percentiles)
- Age (in months) at first dose or nominal visit = [(first dose date or nominal visit date – informed consent date + age at IC (in days)]/30.4375 (demographics/baseline characteristics)
- Age (in months) at first dose or nominal visit = [(first dose date or nominal visit date – informed consent date + age at IC (in days)] (for z-scores)

2. Missing first dose date or last dose date:

- If the first dose date is missing, use the Day 1 visit date to impute.
- If the last dose date is missing or a partial date is reported, the last dose date will be imputed based on, in descending order of priority, the ETT visit date, the last visit date before the SFU visit, or the last study

drug administration date from the EC SDTM domain, as appropriate. The imputation algorithm will ensure the imputed last dose date does not exceed the study participation end date.

3. Sweat Chloride:

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

▪ 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 (to impute in practice, use the informed consent date).
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 (to impute in practice, use the end of study date).

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

Table 12-1 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 treatments/procedures will follow the same imputation rule.

▪ Appendix C: 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 date, the AE start date will be imputed using the study informed consent date.

- **If only Day of AE start date is missing:**
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then:
        - If AE start Year and Month are equal to the month and year of first dose date of the Treatment Period, then impute the AE start Day as the day of first dose date of the Treatment Period;
        - Else, impute the AE start Day as 1.
    - Else, impute the AE start Day as 1.

  Compare the imputed AE start date with the TE Period to determine whether the AE is pretreatment AE, TEAE, or post-treatment AE.
- **If Day and Month of AE start date are missing:**
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then:
        - If AE start Year is equal to the year of first dose date of the Treatment Period, then impute the AE start Month and Day as the month and day of first dose date of the Treatment Period;
        - Else, impute the AE start Month as January and Day as 1.
    - Else, impute the AE start Month as January and Day as 1.

  Compare the imputed AE start date with the TE period to determine whether the AE is pretreatment AE, TEAE, or post-treatment AE.
- **If Year of AE start date is missing:**

  If the year of AE start is missing or AE start date is completely missing, then query site and:
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then impute the AE start date as the first dose date of the Treatment Period;
    - Else, impute the AE start date as the informed consent date.

All imputation should ensure that the imputed AE start date is not before the informed consent date.

Imputation rules for partial AE end dates are defined as follows: Impute the AE end date as min (the last day of the month, end of study participation) if Day is missing, or min (December, end of study participation) if Month is missing.

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

Table 12-2 Threshold Analysis Criteria for Laboratory Tests (as applicable)

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

Table 12-2 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Gamma-Glutamyl Transferase (GGT)	>ULN - ≤2.5xULN >2.5x - ≤5xULN >5x - ≤20xULN >20xULN	CTCAE grade 1-4
Clinical Chemistry (NON-LFT)		
Albumin	<LLN	CTCAE grade 1-3
Amylase	>ULN - ≤1.5xULN >1.5x - ≤2xULN >2x - ≤5xULN >5xULN	Criteria based upon CTCAE
Creatinine	>ULN - ≤1.5xULN >1.5x - ≤3xULN >3x - ≤6xULN >6xULN	CTCAE grades 1-4
Lipase	>ULN - ≤1.5xULN >1.5x - ≤2xULN >2x - ≤5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
Creatine Kinase	>ULN - ≤2.5xULN >2.5x - ≤5xULN >5x - ≤10xULN >10xULN	CTCAE grades 1-4
Hematology		
Hemoglobin	Hgb decreased (anemia) <LLN - ≥100 g/L <100 – ≥80 g/L <80 g/L	CTCAE grade 1-3
	Hgb increased >ULN - ≤20 g/L above ULN >20 g/L above ULN - ≤40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3
Platelets	Platelet decreased <LLN - ≥75 x 10e9/L <75.0 – ≥50 x 10e9/L <50.0 – ≥25 x 10e9/L <25 x 10e9/L	CTCAE grade 1-4
	Platelet increased >ULN	No CTCAE available

Table 12-2 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Reticulocytes/Erythrocytes (%)	<LLN >ULN	No CTCAE
Coagulation		
Activated partial thromboplastin time (aPTT)	>ULN - ≤1.5xULN >1.5x – ≤2.5xULN >2.5xULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤1.5xULN >1.5x – ≤2.5xULN >2.5xULN	CTCAE grade 1-3

Table 12-3 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
Heart Rate	Bradycardia: <90 beats/min Tachycardia: ≥150 beats/min	
PR Interval	>150 msec	
QRS Duration	≥80 msec	
QTcF Interval	≥450 msec >500 msec Increase from baseline >60 msec	To be applied to any kind of QT correction formula.

Table 12-4 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
SBP	≥95th percentile at least once	See Appendix E: Criteria for Threshold Analysis on SBP and DBP for details
DBP	≥95th percentile at least once	See Appendix E: Criteria for Threshold Analysis on SBP and DBP for details
Weight	Weight gain: ≥5% increase from baseline Weight loss: ≥5% decrease from baseline	

▪ Appendix E: Criteria for Threshold Analysis on SBP and DBP

The percentiles for SBP and DBP threshold criteria in Table 12-5Grouped Percentiles for length/height-for-age percentiles are adjusted for gender, age, and length/height. The values are provided in the table on the National Heart, Lung, and Blood Institute (NHLBI) website (https://www.nhlbi.nih.gov/files/docs/guidelines/child_tbl.pdf) [Accessed Aug 2025].

For the implementation of the table, the grouped length/height-for-age percentiles are determined based on the calculated length/height-for-age percentiles, using the rules in Table 12-5Grouped Percentiles for length/height-for-age percentiles.

Table 12-5 Grouped Percentiles for length/height-for-age percentiles

Calculated Percentiles (%)	Grouped Percentiles (%)
0 – <7.5	5
7.5 – <17.5	10
17.5 – <37.5	25
37.5 – <62.5	50
62.5 – <82.5	75
82.5 – <92.5	90
92.5 – 100	95

