*VERTEX PHARMACEUTICALS INCORPORATED*

# Statistical Analysis Plan (Methods)

## Protocol Number VX20-445-111, Version 3.0

**A Phase 3 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Elexacaftor/Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 Through 5 Years of Age**

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**Version: 2.0**
**Version Date of SAP: 02 May 2022**

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# 2 LIST OF ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| [redacted] | [redacted] |
| bpm | beats per minute |
| CF | cystic fibrosis |
| *CFTR* | cystic fibrosis transmembrane conductance regulator protein or the gene encoding the protein. |
| CI | confidence interval |
| CRF | case report form |
| CRO | contract research organization |
| CSP | clinical study protocol |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| ELX | elexacaftor |
| FAS | full analysis set |
| FDC | fixed-dose combination |
| *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 |
| IVA | ivacaftor |
| LCI | lung clearance index |
| LS means | least squares means |
| LFT | liver function test |
| max | maximum value |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MF | minimal function |
| MFHS | modified facial hedonic scale |
| min | minimum value |
| MMRM | mixed model repeated measure |
| N | number of subjects |
| PD | pharmacodynamic/pharmacodynamics |
| PK | pharmacokinetic/pharmacokinetics |
| PT | preferred term |
| q12h | every 12 hours |
| QRS | Q, R, and S-wave define the QRS-complex in an ECG |
| QT | QT interval |
| QTc | QT interval corrected for heart rate |
| QTcF | QT interval corrected for heart rate with Fridericia's correction |

| Abbreviation | Term |
|---|---|
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SE | standard error |
| SOC | system organ class |
| SwCl | sweat chloride |
| TC | triple combination |
| TEAE | treatment-emergent adverse event |
| TEZ | tezacaftor |
| ULN | upper limit of normal |
| WHODrug | World Health Organization Drug Dictionary Enhanced |

[redacted]

# 4 INTRODUCTION

Study VX20-445-111 (Study 445-111) is a Phase 3, 2-part (Parts A and B), multicenter study evaluating the safety, tolerability, and pharmacokinetics (PK) of elexacaftor (ELX, VX-445) in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects 2 through 5 years of age (inclusive) with cystic fibrosis (CF). Part B will initiate after the completion of Part A. Safety, tolerability, and available PK data from Part A will be reviewed by Vertex to confirm or adjust the dose(s) chosen for Part B.

To provide analysis of the safety and tolerability data for Part A, the previous statistical analysis plan (SAP, Version 1.0, dated 01 FEB 2021) was finalized and approved before data lock of Part A. This SAP (Version 2.0) is a preplanned amendment to provide analysis of the safety and efficacy data for Part B. All changes from SAP Version 1.0 are made to Part B analysis only. Any revisions to this approved SAP will be documented and approved in an amendment to this SAP.

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.

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, and IVA when dosed in TC
- 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, and IVA
- 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
- Absolute change in lung clearance index $(LCI)_{2.5}$ from baseline through Week 24

[redacted]

# 7 STUDY DESIGN

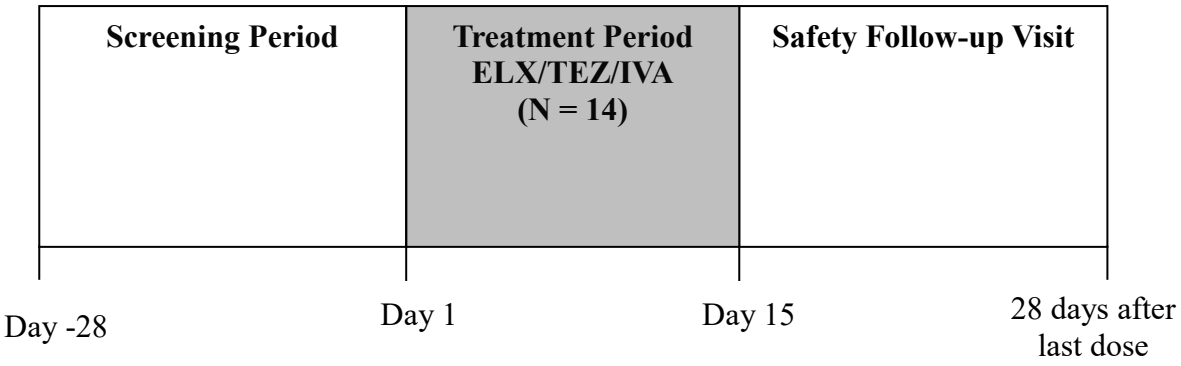
## 7.1 Overall Design

This is a Phase 3, 2-part (Parts A and B), multicenter study evaluating the safety, tolerability, PK, PD, and efficacy of ELX/TEZ/IVA in CF subjects 2 through 5 years of age (inclusive).

**Part A**

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

**Figure 7-1 VX20-445-111 Part A Study Design**



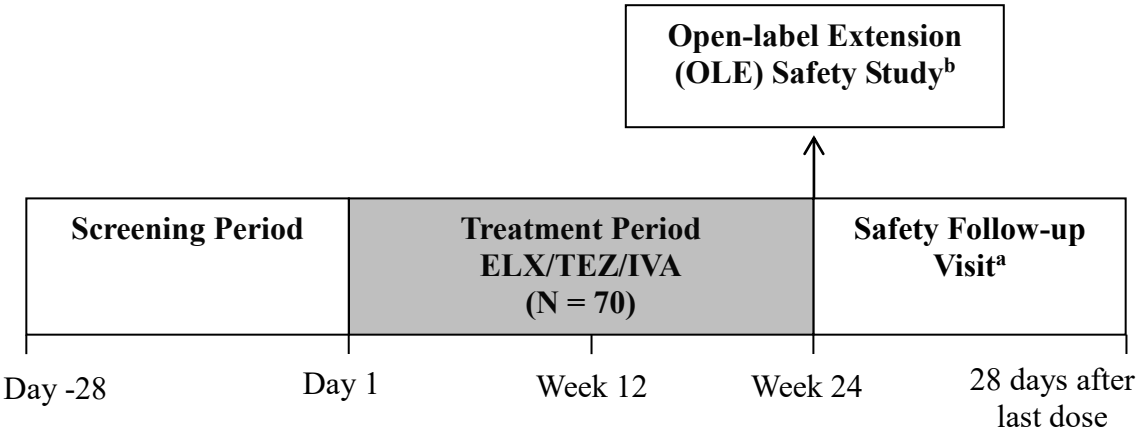

ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor
Note: ELX/TEZ/IVA will be administered from Day 1 through Day 15. On Day 15, only the morning dose will be administered.

**Part B**

A schematic of the study design for Part B is provided in **Figure 7-2**. Part B will initiate after available data from Part A has been reviewed by Vertex and the Part B dose(s) has been confirmed or adjusted. Part B will enroll approximately 70 subjects, of which at least 30 subjects will have F/MF genotypes and at least 15 subjects with the F/F genotype. At least 25 subjects should be between 2 and 3 years of age (inclusive). During the Treatment Period, subjects will be administered ELX/TEZ/IVA (**Table 7-1**) for approximately 24 weeks.

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

**Figure 7-2 VX20-445-111 Part B Study Design**




ELX: elexacaftor; IVA: ivacaftor; 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 Parts A and B Doses**

| Subject Weight at Day 1 | ELX Dose | TEZ Dose | IVA Dose |
|---|---|---|---|
| **Part A** | | | |
| ≥14 kg only | 100 mg qd | 50 mg qd | 75 mg q12h |
| **Part B** | | | |
| ≥14 kg | 100 mg qd | 50 mg qd | 75 mg q12h |
| ≥10 kg to <14 kg | 80 mg qd | 40 mg qd | 60 mg qAM<br>59.5 mg qPM |

ELX: elexacaftor; IVA: ivacaftor; qAM: once every morning; qd: once daily; qPM: once every evening; q12h: every 12 hours; 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 M23-445 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% CI within 60% and 140% of the geometric mean estimate of clearance for ELX and M23-445.

### Part B

No formal power calculation is performed. The number of subjects in Part B is deemed adequate to meet the primary safety objective. The planned enrollment is approximately 70 subjects. Assuming a dropout rate of 10% or 20%, approximately 63 or 56 subjects, respectively, are expected to complete Part B. Incidence of AEs is a safety endpoint. **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% |
|---|---|---|
| 56 | 94.3% | 99.7% |
| 63 | 96.1% | 99.9% |

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

**Part A and Part B**

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 for this study) or receive at least 1 dose of study drug. This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

## 8.2 Safety Set

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

## 8.3 Full Analysis Set

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

# 9 STATISTICAL ANALYSIS

## 9.1 General Considerations

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

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

**Continuous variables** will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), median, minimum value (min), and maximum value (max).

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

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

Note: in Part B, for subjects who take CFTR modulators (e.g., Orkambi) during the 28 days before the screening visit, the data collected at the screening visit will not be used for baseline derivation for sweat chloride and LCI.

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

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

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

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

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

**Visit windowing rules** for protocol-defined visits in Part A are provided in Appendix A.

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

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

## 9.2 Background Characteristics

### 9.2.1 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
- FAS

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

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

Demographic data will include the following:

- Age at baseline (in years)
- Sex (male, female)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, and not collected per local regulations)

Baseline characteristics will include the following:

- CFTR genotype group (F/F, F/MF)

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

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

#### 9.2.1.3 Medical History

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

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

#### 9.2.1.4 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 the corresponding Part of the study.
- **Concomitant medication:** medication continued or newly received during the corresponding TE period.
- **Post-treatment medication:** medication continued or newly received after the corresponding TE period.

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

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

Concomitant medications will be summarized descriptively for the FAS using frequency tables by: 1) preferred name (PN); and 2) anatomic class (ATC) level 1, ATC level 2, and PN. 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 – first dose date + 1 day, 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 using counts and percentages for Treatment Period categories. The categories are specified as: ≤2 days; >2 and ≤4 days; >4 and ≤8 days; >8 and ≤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 FAS.

Study drug compliance will be calculated as: $100 \times [1 - (\text{total number of days of study drug interruption}) / (\text{duration of study drug exposure in days})]$. 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.

#### 9.2.1.7 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.

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 based on the All Subjects Set:

- All Subjects Set
- Safety Set
- FAS

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

- Completed treatment
- Prematurely discontinued treatment and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation
- Rolled over to the 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 based on the FAS.

Demographic data will include the following:

- Age at baseline (in years)
- Age group at screening (≥2 to <3, ≥3 to <4, ≥4 to <5, and ≥5 to <6 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:

- CFTR genotype group (F/F, F/MF, Other)
- Weight group (<14 kg, and ≥14 kg)

Disease characteristics will include the following:

- Sweat chloride at baseline (continuous)
- $LCI_{2.5}$ at baseline (continuous)
- Prior use of CFTR modulator (Yes, No)
- Prior use of dornase alfa (Yes, No)
- Prior use of azithromycin (Yes, No)
- Prior use of inhaled antibiotic (Yes, No)
- Prior use of any bronchodilator (Yes, No)
- Prior use of any inhaled bronchodilator (Yes, No)
- Prior use of any inhaled hypertonic saline (Yes, No)
- Infection with *Pseudomonas aeruginosa* within 2 years prior to screening (Positive, Negative)

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

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

#### 9.2.2.3 Medical History

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

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

#### 9.2.2.4 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 Part B.
- **Concomitant medication:** medication continued or newly received during the TE period in Part B.
- **Post-treatment medication:** medication continued or newly received after the TE period in Part B.

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

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

Concomitant medications will be summarized descriptively for the FAS using frequency tables by: 1) preferred name (PN); and 2) anatomic class (ATC) level 1, ATC level 2, and PN. Prior medications will also be summarized the same way as concomitant medications. 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 – first dose date in Part B + 1 day, 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 using counts and percentages for Treatment Period categories. The categories are specified as: ≤15 days; >15 days and ≤4 weeks; >4 and ≤8 weeks; >8 and ≤12 weeks; >12 and ≤16 weeks; >16 and ≤20 weeks; >20 and ≤24 weeks; >24 weeks. Additionally, the total study drug exposure, defined as the sum total of the study drug exposure across all subjects in patient-weeks 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. In addition, a study drug interruption that continues through the end of the study participation (i.e., subject does not resume study drug before the end of the study participation) will not be included in the compliance calculation.

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

#### 9.2.2.7 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.

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

## 9.3 Efficacy Analysis

### 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

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

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

#### 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 (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.

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

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

#### 9.3.2.2.2 Analysis Method

Absolute change in sweat chloride from baseline through Week 24:

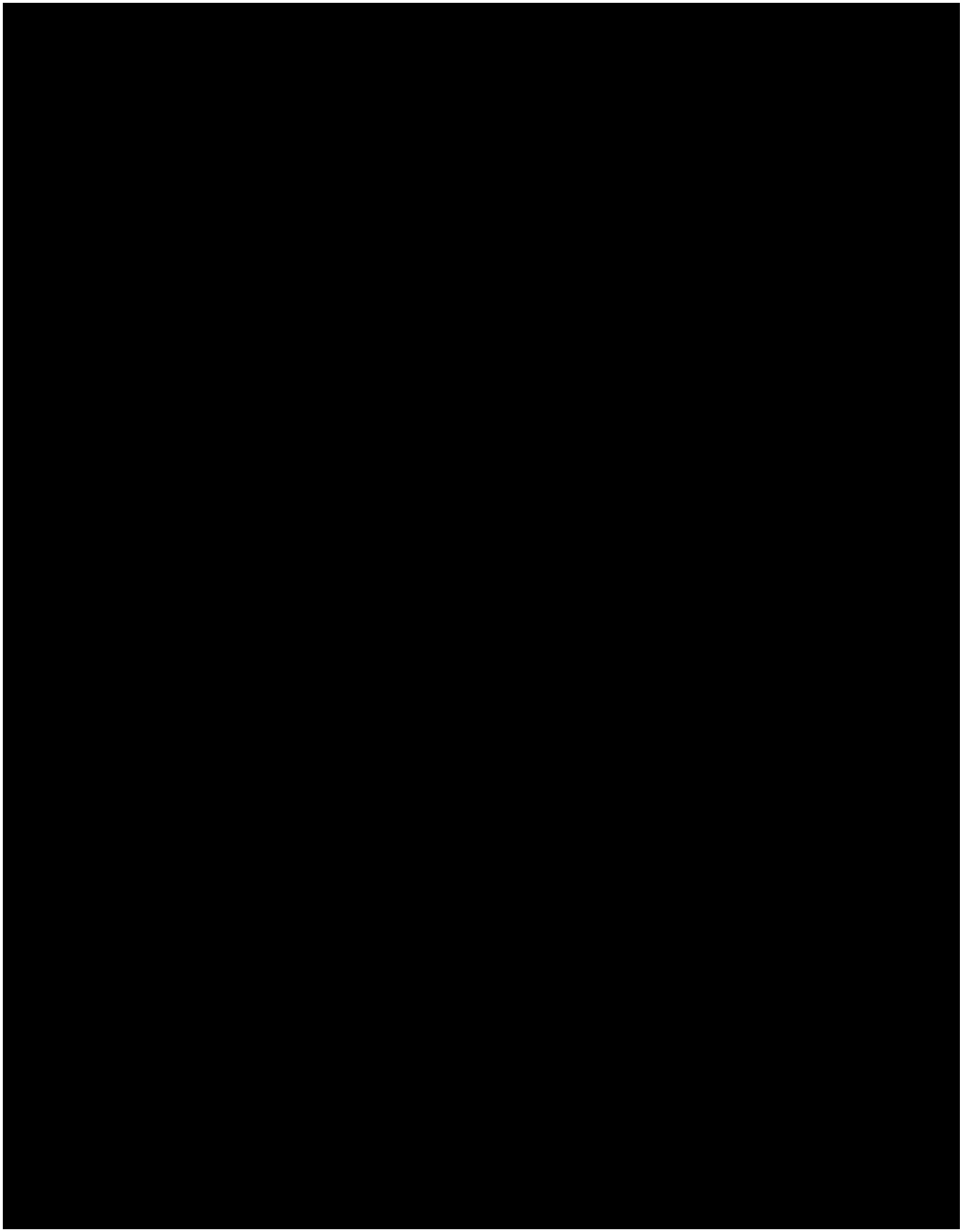
Absolute change from baseline in sweat chloride will be analyzed using a mixed-effects model for repeated measures (MMRM) approach based on the FAS. The MMRM will be used to estimate the within-group mean absolute change in sweat chloride through Week 24. The model will include absolute change from baseline in sweat chloride (including all measurements up to and including Week 24) as the dependent variable, and visit as the fixed effect, with baseline sweat chloride value and genotype group (F/F vs F/MF) as covariates. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the *F*-test of fixed effects will be estimated using the Kenward-Roger approximation[2]. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, a compound symmetry covariance structure will be used instead. Conditional on the observed data and covariates, missing data will be assumed to be missing at random; consequently, no imputation of missing data will be performed.

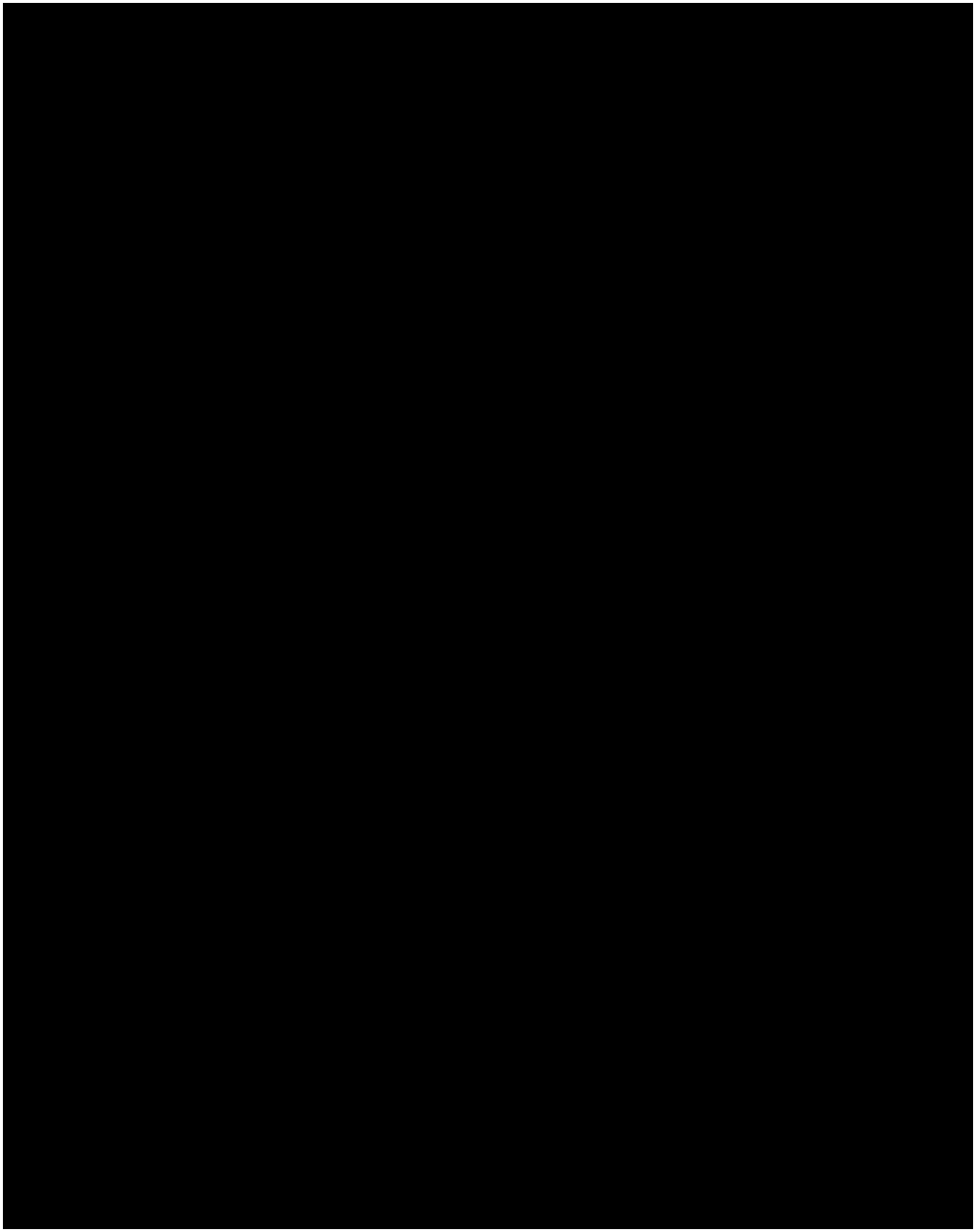
The results obtained from the model will be the average treatment effect through Week 24, estimated using all post-baseline visits up to and including Week 24. The estimated mean change from baseline in sweat chloride through Week 24, along with the corresponding 2-sided 95% confidence interval (CI) and *P*-value, will be provided.

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

Analysis of this variable will be based on an MMRM similar to the analysis of the absolute change in sweat chloride from baseline through Week 24, with the baseline $LCI_{2.5}$ included as a covariate instead of baseline sweat chloride. The analysis will be based on subjects in the FAS who have performed MBW as an assessment at least once.

To better assess the longitudinal profile of sweat chloride and $LCI_{2.5}$ with repeated measures up to Week 24, the LS mean (SE) of the change from baseline at each post-baseline visit along with the 95% CI will be estimated from the corresponding MMRM. The LS mean (SE) at each visit will also be plotted. In addition, the post-baseline raw values and the absolute change from baseline at each post-baseline visit will be summarized descriptively (n, mean, SD, median, minimum, and maximum).





[redacted]

#### 9.3.2.4 Sensitivity Analysis

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

[redacted]

## 9.4 Safety Analysis

### 9.4.1 Safety Analysis for Part A

Safety is one of the primary objectives of Part A. All safety analyses will be conducted based on data from the TE period in 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 at or after the first dose of study drug through the end of the TE period in the corresponding Part.
- **Post-treatment AE:** any AE that worsened (either in severity or seriousness) or that was newly developed after the TE period in the corresponding Part.

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

Details for imputing missing or partial start dates of adverse events are defined in Appendix 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 leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Serious TEAEs

- TEAEs leading to death
- Grade 3/4/5 TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- Related 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). When summarizing the number and percentage of subjects, subjects with multiple occurrences of the same AE or a continuing AE will be counted once and only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries.

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

- All TEAEs by PT

All AEs, including pretreatment AEs, TEAEs, and post-treatment AEs, will be presented in an individual subject data listing based on the All Subjects Set. In addition, a listing containing individual subject adverse event data for TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, Grade 3/4/5 TEAEs, 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 the treatment-emergent laboratory assessments, the observed values and change from baseline values of the continuous hematology, coagulation and chemistry results will be summarized in SI units at each visit.

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

Results of urinalysis will be listed in individual subject data listings only. In addition, a listing containing individual subject hematology, chemistry, and coagulation values will be provided. This listing will include data from both scheduled and unscheduled visits.

#### 9.4.1.3 Electrocardiogram

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

The number and percentage of subjects meeting at least 1 threshold analysis criterion for selected parameters during the TE period will be summarized. The threshold analysis criteria are provided in Appendix 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 the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized at each visit. The following vital signs parameters will be summarized: [redacted] systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (breaths per minute), and respiratory rate (breaths per minute).

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

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

#### 9.4.1.5 Pulse Oximetry

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

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

#### 9.4.1.6 Ophthalmologic Examinations

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

#### 9.4.1.7 Physical Examination

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

#### 9.4.1.8 Visit Type

A listing containing the impact of COVID-19 pandemic on subjects' visits will be provided.

[redacted]

### 9.4.2 Safety Analysis for Part B

Safety is the primary objective of Part B. All safety analyses will be conducted 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.

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

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 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 leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Serious TEAEs
- TEAEs leading to death
- Grade 3/4/5 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). When summarizing the number and percentage of subjects, subjects with multiple occurrences of the same AE or a continuing AE will be counted once and only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries.

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

- All TEAEs by PT

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

#### 9.4.2.2 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.

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

Results of urinalysis will be listed in individual subject data listings only. In addition, a listing containing individual subject hematology, chemistry, and coagulation values will be provided. This listing will include data from both scheduled and unscheduled visits.

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.

When summarizing laboratory values at a visit, local laboratory values will be used if no central laboratory value is available. When deriving threshold analysis criterion and maximum treatment-emergent values, both local laboratory values and central laboratory values will be included.

#### 9.4.2.3 Electrocardiogram

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

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

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

#### 9.4.2.4 Vital Signs

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

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

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

#### 9.4.2.5 Pulse Oximetry

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

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

#### 9.4.2.6 Ophthalmologic Examinations

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

#### 9.4.2.7 Physical Examination

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

#### 9.4.2.8 Visit Type

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

[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 IDMC Statistical Analysis Plan.

# 11 REFERENCES

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

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

# 12 LIST OF APPENDICES

## Appendix A: Analysis Visit Windows for Safety and Efficacy Assessments

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

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

[redacted]

Notes:

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

[2] The analysis visit windows will be applied using the following rules for both scheduled and unscheduled visits:

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

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

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

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

[redacted]

Derived Variables:

1. Age (in years) at first dose date and nominal visit (for demographics and listing):

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

   Obtain the informed consent/assent date.

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

2. Age (in months) at nominal visit [redacted]

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

   Obtain the informed consent/assent date.

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

3. Missing first dose date or last dose date

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

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

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

| Assessment | Visit[1] | Target Study Day | Analysis Visit Window (in study days)[2, 3, 4,5] |
|---|---|---|---|
| **Safety Assessment** | | | |
| • Serum Chemistry | Day 1 (Baseline) | 1 | ≤1 Pre-dose |
| | Day 15 | 15 | [1, 22] |
| | Week 4 | 29 | (22, 43] |
| | Week 8 | 57 | (43, 71] |
| | Week 12 | 85 | (71, 99] |
| | Week 16 | 113 | (99, 127] |
| | Week 20 | 141 | (127, 155] |
| | Week 24 | 169 | (155, 197] |
| | Safety Follow-up | Not applicable | Use nominal visit |
| • Hematology | Day 1 (Baseline) | 1 | ≤1 Pre-dose |
| | Day 15 | 15 | [1, 22] |
| | Week 4 | 29 | (22, 43] |
| | Week 8 | 57 | (43, 71] |
| | Week 12 | 85 | (71, 99] |
| | Week 16 | 113 | (99, 141] |
| | Week 24 | 169 | (141, 197] |
| | Safety Follow-up | Not applicable | Use nominal visit |
| • Coagulation | Day 1 (Baseline) | 1 | ≤1 Pre-dose |
| | Week 24 | 169 | [1, 197] |
| | Safety Follow-up | Not applicable | Use nominal visit |
| • Vital Signs [redacted] | Day 1 (Baseline) | 1 | ≤1 |
| • Pulse oximetry | Day 15 | 15 | [1, 22] |
| | Week 4 | 29 | (22, 43] |
| | Week 8 | 57 | (43, 71] |
| | Week 12 | 85 | (71, 99] |
| | Week 16 | 113 | (99, 141] |
| | Week 24 | 169 | (141, 197] |
| | Safety Follow-up | Not applicable | Use nominal visit |
| • Standard 12-lead ECG | Day 1 (Baseline) | 1 | ≤1 Pre-dose |
| | Day 15 | 15 | [1, 50] |
| | Week 12 | 85 | (50, 127] |
| | Week 24 | 169 | (127, 197] |
| | Safety Follow-up | Not applicable | Use nominal visit |
| **Efficacy Assessment and Pharmacodynamic Assessment** | | | |
| [redacted] | | | |

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

| Assessment | Visit[1] | Target Study Day | Analysis Visit Window [2, 3, 4,5] |
|---|---|---|---|
| [redacted] | | | |
| • Sweat Chloride<br>• Lung Clearance Index | Day 1 (Baseline)<br>Week 4<br>Week 12<br>Week 24 | 1<br>29<br>85<br>169 | ≤1 Pre-dose<br>(1, 57]<br>(57, 127]<br>(127, 197] |
| [redacted] | | | |

Notes:

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

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

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

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

[5] For efficacy analysis of Part B, if there is Safety Follow-up visit with study day > 197, the nominal Safety Follow-up visit will be mapped to the Safety Follow-up analysis visit. Else, if there is ETT visit with study day > 197, the ETT visit will be mapped to the Safety Follow-up analysis visit. Else, if there are multiple assessments with study days >197, then select the earliest record.

Derived Variables:

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

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

Obtain the informed consent/assent date.

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

2. Age (in months) at nominal visit [redacted]

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

   Obtain the informed consent/assent date.

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

3. Missing first dose date or last dose date

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

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

4. Sweat Chloride:

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

5. Electrocardiogram:

   Baseline will be defined as the most recent non-missing measurement (or the average, for example, if the most recent non-missing measurement is obtained in triplicate), before the first dose of study drug in the Treatment Period. If multiple ECG measurements are obtained on the same calendar day during the TE period,

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

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

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

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date (to impute in practical, use the informed consent/assent date to impute).
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last day of the month.
    b. If DAY and Month are both missing, use the last day of the year.
    c. If DAY, Month and year are all missing, assign 'continuing' status to stop date (in practical, use the End of Study Date to impute).

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

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

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

P: Prior; C: Concomitant; A: Post

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

## Appendix C: Imputation Rules for Missing AE Dates

Imputation rules for missing or partial AE start date are defined below. If the imputed AE start date is before the study informed consent/assent date, the AE start date will be imputed using the study informed consent/assent date.

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

  Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

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

  Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

- **If Year of AE start date is missing:**

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

Imputation rules for partial AE end date are defined below:

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

## Appendix D: Criteria for Threshold Analysis

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

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

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

| Parameter | Threshold Analysis | Comments |
|---|---|---|
| AST and Total Bilirubin | AST>3xULN and TBILI>2xULN | FDA DILI Guidance Jul 2009. |
| (ALT or AST) and Total Bilirubin | (ALT>3xULN or AST>3xULN) and TBILI>2×ULN | FDA DILI Guidance Jul 2009. |
| GGT | >ULN - ≤2.5xULN<br>>2.5x - ≤5xULN<br>>5x - ≤20xULN<br>>20xULN | CTCAE grade 1-4 |
| **Clinical Chemistry (NON-LFT)** | | |
| Albumin | <LLN | CTCAE grade 1-3 |
| Amylase | >ULN - ≤1.5xULN<br>>1.5x - ≤2xULN<br>>2x - ≤5xULN<br>>5xULN | Criteria based upon CTCAE |
| Creatinine | >ULN - ≤1.5xULN<br>>1.5x - ≤3xULN<br>>3x - ≤6xULN<br>>6xULN | CTCAE grades 1-4 |
| Lipase | >ULN - ≤1.5xULN<br>>1.5x - ≤2xULN<br>>2x - ≤5xULN<br>>5xULN | Criteria based upon CTCAE |
| Total protein | <LLN<br>>ULN | No CTCAE |
| Creatine kinase | >ULN - ≤2.5xULN<br>>2.5x - ≤5xULN<br>>5x - ≤10xULN<br>>10xULN | CTCAE grades 1-4 |
| **Hematology** | | |
| Hemoglobin | Hgb decreased (anemia)<br><LLN - ≥100 g/L<br><100 - ≥80 g/L<br><80 g/L | CTCAE grade 1-3 |
| | Hgb increased<br>>ULN - ≤20 g/L above ULN<br>>20 g/L above ULN - ≤40 g/L above ULN<br>>40 g/L above ULN | CTCAE grade 1-3 |

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

| Parameter | Threshold Analysis | Comments |
|---|---|---|
| Platelets | Platelet decreased<br><LLN - ≥75 x 10e9 /L<br><75 - ≥50 x 10e9 /L<br><50 - ≥25 x 10e9 /L<br><25 x 10e9 /L | CTCAE grade 1-4 |
| | Platelet increased<br>>ULN | No CTCAE available |
| Reticulocytes/Erythrocytes (%) | <LLN<br>>ULN | No CTCAE |
| **Coagulation** | | |
| Activated partial thromboplastin time (PTT) | >ULN - ≤1.5xULN<br>>1.5 - ≤2.5xULN<br>>2.5xULN | CTCAE grade 1-3 |
| Prothrombin time (PT) International Normalized Ratio (INR) | >ULN - ≤1.5xULN<br>>1.5 - ≤2.5xULN<br>>2.5 x ULN | CTCAE grade 1-3 |

**Table 12-5 Threshold Analysis Criteria for ECGs**

| Parameter | Threshold Analysis | Comments |
|---|---|---|
| HR | Bradycardia<br><55 bpm | |
| | Tachycardia<br>>134 bpm | |
| PR | >180 ms and increase from baseline ≥20 ms | |
| QRS | >89 ms | |
| QTc | Absolute values (ms)<br>>449 ms<br>≥500 ms<br><br>Increase from baseline<br>Increase from baseline >60 ms | To be applied to any kind of QT correction formula. |

**Table 12-6 Threshold Analysis Criteria for Vital Signs**

| Parameter | Threshold Analysis | Comments |
|---|---|---|
| SBP | ≥95 percentile | See Appendix E for details |
| DBP | ≥95 percentile | See Appendix E for details |
| Weight | Weight gain<br>≥5% increase from baseline | |

**Table 12-6 Threshold Analysis Criteria for Vital Signs**

| Parameter | Threshold Analysis | Comments |
|---|---|---|
| | Weight loss<br>≥5% decrease from baseline | |

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

The percentiles for SBP and DBP threshold criteria in Table 12-6 are adjusted for gender, age and 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 Oct 28, 2020].

For the implementation of the table, the grouped height-for-age percentiles are determined based on the calculated height-for-age percentiles, using the rules in Table 12-7.

**Table 12-7 Grouped Percentiles for 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 |