1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX20-445-126 Version 1.0 (Final Analysis)

A Phase 3b Open-label Study Evaluating the Effects of Elexacaftor/Tezacaftor/Ivacaftor on Cough and Physical Activity in Cystic Fibrosis Subjects 12 Years of Age and Older Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)

Authors of SAP: [redacted]

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[redacted]

4 INTRODUCTION

Study VX20-445-126 (Study 445-126) is a Phase 3b open-label study evaluating the efficacy of elexacaftor (ELX, VX-445) in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) on cough and physical activity using wearable devices in subjects 12 years of age (inclusive) and older with cystic fibrosis (CF) who are heterozygous for *F508del* and a minimal function mutation (F/MF).

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

This SAP (Methods) documents the planned statistical analyses of efficacy and [redacted] defined in the VX20-445-126 study protocol. It also documents analyses for additional efficacy and safety variables not specified in the protocol, which will provide supportive information for the scientific understanding of the drug entity.

The Vertex Biometrics Department will perform the statistical analysis of efficacy and [redacted]; SAS (Version 9.4 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the clinical database lock. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP.

5 STUDY OBJECTIVES

To evaluate the effects of ELX/TEZ/IVA on cough and physical activity using wearable technology

6 STUDY ENDPOINTS

6.1 Primary Endpoint

- Percent reduction from baseline in cough frequency (cough events per day) to the average of Week 8 through Week 12

6.2 Secondary Endpoint

- Absolute change from baseline in total step count per day to the average of Week 8 through Week 12

[redacted]

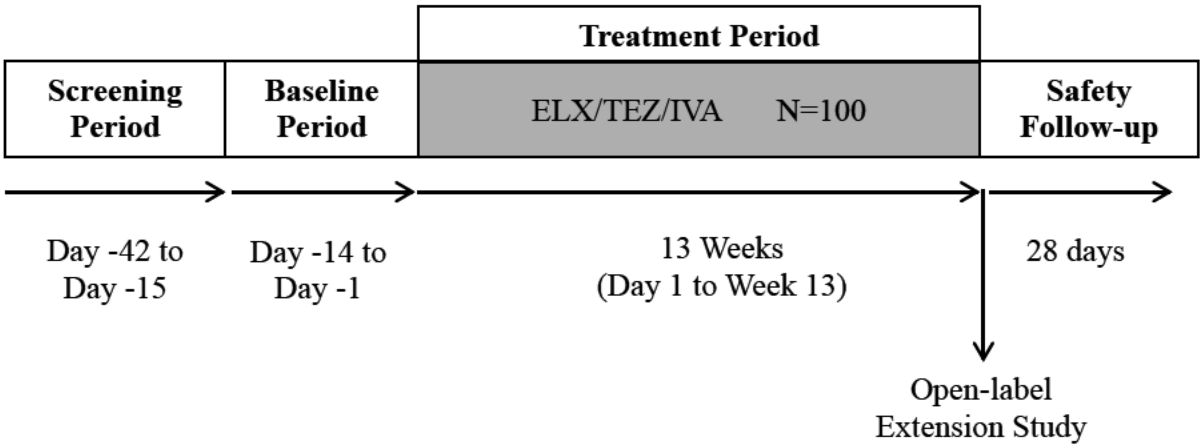
[redacted]

7 STUDY DESIGN

7.1 Overall Design

This is a Phase 3b, open-label study evaluating the effects of ELX/TEZ/IVA on cough and physical activity using wearable technology. A schematic of the study design is shown in Figure 7-1. All subjects will receive ELX 200 mg once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) for approximately 13 weeks. A treatment duration of approximately 13 weeks allows the efficacy endpoints to be collected with wearable devices through Week 12 (i.e. a complete, 24-hour cough assessment during Week 12 and at least 12 complete weeks of continuous actigraphy measures in the treatment period). The Week 13 clinic visit is for operational purposes, at which patients return the wearable devices and complete any in-clinic assessments. Approximately 100 subjects will be enrolled.

Figure 7-1 VX20-445-126 Study Design



ELX: elexacaftor; IVA: ivacaftor; N: total sample size; TEZ: tezacaftor
Notes: Subjects who are eligible will be offered the opportunity to enroll in an open-label extension safety study evaluating ELX/TEZ/IVA. The Safety Follow-up Visit is not required for subjects who complete the Week 13 Visit and have enrolled in the open-label extension study, or who transition to a commercially available CFTR modulator regimen, within 28 days

7.2 Sample Size and Power

The primary efficacy endpoint is percent reduction from baseline in cough frequency (cough events per day) to the average of Week 8 through Week 12. Assuming a standard deviation of 1 for the log ratio of cough frequency post-baseline versus baseline, a sample size of approximately 100 subjects will provide 95% confidence intervals (which represents the estimation precision) as shown in Table 7-1 at various observed percent reductions in cough frequency (30%, 40%, and 50%), after accounting for 20% missing. Note: percent reduction equals 100% × (1- ratio of cough frequency post-baseline vs. baseline).

Table 7-1 95% Confidence Intervals for Percent Reduction in Cough Frequency per day from Baseline

Percent reduction in cough frequency	30%	40%	50%
95% Confidence Intervals	(13%, 44%)	(25%, 52%)	(38%, 60%)

30%, 40%, 50% percent reduction corresponds to ratio of 0.7, 0.6 and 0.5 in cough frequency (post-baseline vs. baseline), respectively.

8 ANALYSIS SETS

The following analysis sets are defined: All Subjects Set, Full Analysis Set (FAS) and Safety Set.

8.1 All Subjects Set

The **All Subjects Set** will include all subjects who were enrolled. This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

8.2 Full Analysis Set

The **Full Analysis Set** (FAS) is defined as all enrolled subjects who carry the intended *CFTR* allele mutation and have received at least 1 dose of study drug. The FAS is to be used in efficacy analyses.

8.3 Safety Set

The **Safety Set** is defined as all subjects who have received at least 1 dose of study drug. The Safety Set is to be used for all safety analyses.

9 STATISTICAL ANALYSIS

9.1 General Considerations

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

Categorical variables will be summarized using counts and percentages.

Baseline value, unless specified otherwise, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug.

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

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

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

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

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

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

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

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

9.2 Background Characteristics

9.2.1 Subject Disposition

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

- Enrolled

- Completed study drug treatment
- Prematurely discontinued treatment (i.e., discontinued all study drugs) and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation
- Rollover to the open-label study

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

9.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized based on the FAS.

Demographic data will include the following:

- Age at baseline (in years)
- Sex (female and male)
- 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)
- Country

Baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

Disease characteristics will include the following:

- $ppFEV_1$ at baseline (<30, ≥30 to <40, ≥40 to <70, ≥70 to ≤90, and >90)
- $ppFEV_1$ at baseline (continuous)
- Prior use of dornase alfa (Yes, No)
- Prior use of azithromycin (Yes, No)
- Prior use of inhaled antibiotic (Yes, No)
- Prior use of bronchodilator (Yes, No)
- Prior use of inhaled bronchodilator (Yes, No)
- Prior use of inhaled hypertonic saline (Yes, No)
- Prior use of inhaled corticosteroids (Yes, No)

In addition, data listings will also be provided for:

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

The predicted FEV_1 will be calculated using the Global Lung Function Initiative (GLI)[1]; details are provided in Appendix B.

9.2.3 Medical History

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

9.2.4 Prior and Concomitant Medications

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

- **Prior medication:** any medication that administered during the 56 days before the first dose of study drug.
- **Concomitant medication:** medication continued or newly received during the TE period.
- **Post-treatment medication:** medication continued or newly received after the corresponding TE period.

A given medication may be classified as a prior medication, a concomitant medication, or a post treatment medication; both prior and concomitant; both concomitant and post treatment; or prior, concomitant, and post treatment.

If a medication has a missing or partially missing start/end date or time and if it cannot be determined whether it was taken before the first dose of study drug, concomitantly during the TE Period, or after the TE Period, it will be considered in all 3 categories of prior, concomitant, and post treatment medication. Details for imputing missing or partial start and/or stop dates of medication are described in Appendix C.

Prior medications and concomitant medications during the Treatment Period 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.

The number of subjects who used hormonal therapy concomitantly during the Treatment Period will be summarized based on the Safety Set.

9.2.5 Study Drug Exposure

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

Duration of study drug exposure (in weeks) will be calculated as: (last dose date of study drug – first dose date of study drug + 1)/7, 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 intervals using counts and percentages.

9.2.6 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 drugs on that day. A study drug interruption that continues through the end of the study participation (i.e., subject does not resume study drug before the end of the study participation) will not be included in the compliance calculation.

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.

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

9.3 Efficacy Analysis

Unless otherwise defined, all efficacy analyses described in this section will be based on the FAS.

9.3.1 Analysis of Primary Efficacy Variable

9.3.1.1 Definition of Variable

The primary endpoint is percent reduction from baseline in cough frequency (cough events per day) to the average of Week 8 through Week 12. Percent reduction from baseline will be calculated and expressed in percentage as 100% × (baseline value - post-baseline value)/baseline value (i.e., -relative change)

Cough frequency per day will be measured by a non-invasive, semi-automated, ambulatory cough monitoring system. The device will be used for a single day (defined by 24 continuous hours) at visits specified in Table 3-2 in CSP. The 24-hour assessment is considered valid if there are at least 10 cumulative hours of recording duration while awake, excluding any duration where the recording is identified as muted, flagged, or device not attached, and excluding any duration where the recording ended early.[2] For valid assessments, the cough frequency per day is the total number of cough events in the 24-hour period (excluding any duration where the recording is identified as muted, flagged, or device not attached, and excluding any duration where the recording ended early).

The baseline value is defined as the geometric mean of valid cough measurements prior to the first dose of study drug (e.g., Day -14 and Day -7). If one value is missing or invalid, the non-missing, valid value will be used. If the cough frequency is zero at a given visit, 0.5 will be added to ensure a non-zero number.

9.3.1.2 Primary Analysis

The primary endpoint is the percent reduction from baseline in cough frequency (cough events per day) to the average of Week 8 through Week 12. The primary analysis will be based on a mixed-effects model for repeated measures (MMRM) with change from baseline at each post-baseline visit (Week 2 to Week 12) on the natural log scale (i.e., log(post-baseline) – log (baseline)) as the dependent variable. Note that if cough frequency is zero at any visit, 0.5 will be added in order to ensure a non-zero number for appropriate natural log calculations. The model will include visit as a fixed effect and log baseline cough frequency as a covariate. 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.[3] 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; no additional imputation of missing data will be performed.

The primary result obtained from the model will be the estimated percent reduction in cough frequency from baseline to the average of Week 8 through Week 12 (defined as the average of Weeks 8, 9, 10, 11, 12). Percent reduction will be calculated as 100% × (1-exponential form of LS mean change at the average of Weeks 8 through 12 on the natural log scale from the above MMRM model). The 2-sided 95% confidence intervals will be provided. Furthermore, the estimated percent reduction at each post-baseline week will also be provided. The estimated percent reduction at each post-baseline week up to Week 12 will be plotted.

The geometric mean and geometric SD of the raw values at baseline and each post-baseline visit up to Week 12 will also be summarized. In addition, daytime and overnight cough frequency per hour will be summarized in a similar way. If the daytime or overnight cough frequency per hour is zero at a given visit, 0.5/24 will be added to ensure a non-zero number.

[redacted]

9.3.2 Analysis of Secondary Efficacy Variable

9.3.2.1 Definition of Variables

The secondary endpoint is the absolute change from baseline in total step count per day to the average of Week 8 through Week 12.

Total step count per day will be measured by the wrist-worn actigraphy sensor on each calendar day. The wrist-worn device will be worn 24 hours per day continuously from Day -14 throughout the Treatment Period. The daily assessment is considered as valid if there are at least 10 cumulative hours of valid wear (excluding periods of non-wear, no data, and artifact [noise]) while awake on that day.[4] The 2-week baseline period and 12-week treatment period will be divided into 14 weekly intervals (Day -14, Day -7, Week 1, Week 2, ..., Week 12), and the average of total step count per valid day will be calculated for each weekly interval, provided that there are valid daily assessments on at least 3 weekdays and 1 weekend day.

The baseline value will be defined as the average of valid weekly interval measurements prior to the first dose of study drug (e.g., average of Day -14 and Day -7). If one weekly interval measurement is missing or invalid, the non-missing, valid interval measurement will be used.

9.3.2.2 Analysis Method

The analysis will be based on an MMRM model similar to the analysis of the primary efficacy variable (without any natural log transformation), with change from baseline at each post-baseline weekly interval (Week 1 to Week 12) as the dependent variable. The model will include the weekly intervals as fixed effects and baseline total step count per day as a covariate.

The primary result obtained from the model will be the estimated mean change from baseline to the average of Week 8 through Week 12. The estimated mean change and 2-sided 95% confidence interval will be provided. Furthermore, the estimated mean change at each post-baseline weekly interval will also be provided. The estimated mean change at each post-baseline weekly interval up to Week 12 will be plotted.

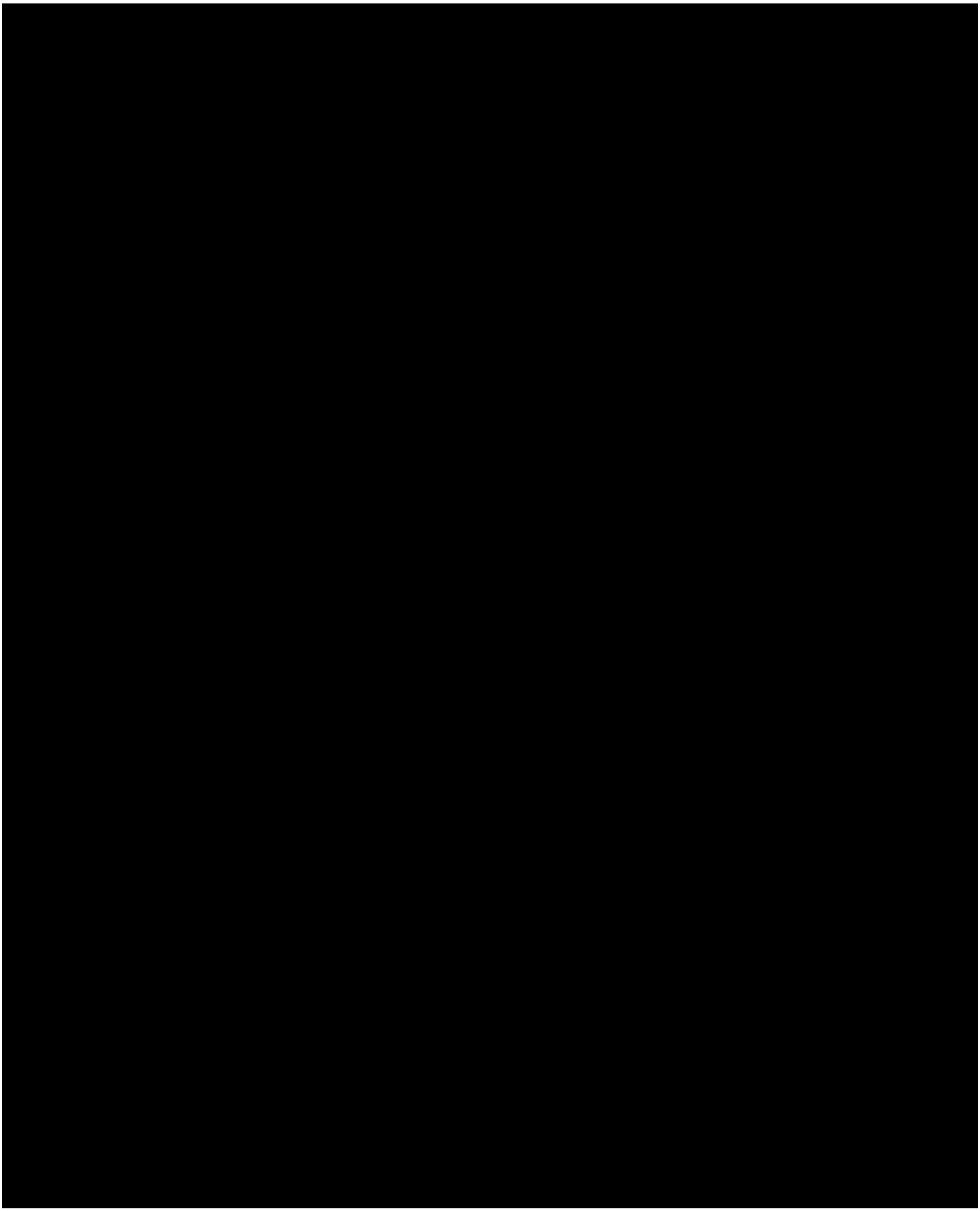
In addition, the post-baseline raw values and the change from baseline at each post-baseline weekly interval up to Week 12 will be summarized descriptively (n, mean, SD, median, minimum, and maximum).

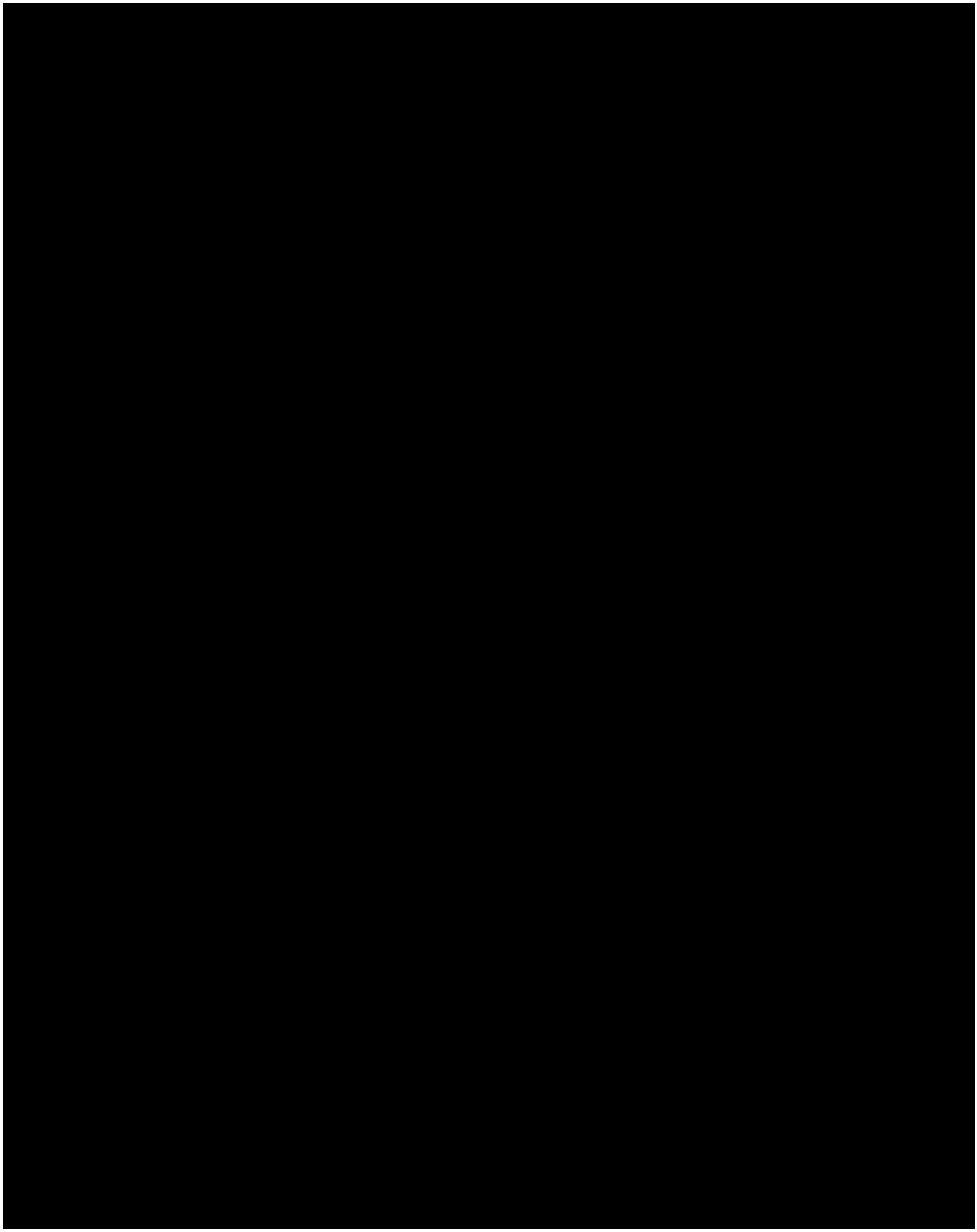
9.3.2.3 Multiplicity Adjustment

Not applicable.

9.3.2.4 Sensitivity Analysis

Not applicable.





[redacted]

9.4 Safety Analysis

All safety analyses will be based on data from the TE period in the Safety Set, unless otherwise specified.

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

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values

[redacted]

Only descriptive analysis of safety will be performed. No statistical testing will be performed. Note that post-baseline safety measurements (except TEAEs) are only scheduled at Week 13.

9.4.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs during the Treatment Period, and post-treatment AEs, defined as follows:

- **Pretreatment AE:** any AE that occurred before the first dose date of study drug.
- **TEAE during the Treatment Period:** any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug through the end of the TE period
- **Post-treatment AE:** any AE that worsened (either in severity or seriousness) or that was newly developed after the TE period.

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

Details for imputing missing or partial start dates of adverse events are described in Appendix D.

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

- Number of TEAEs
- Subjects with any TEAEs
- Subjects with TEAEs by strongest relationship
- Subjects with TEAEs by maximum severity
- Subjects with TEAEs leading to study drug discontinuation
- Subjects with TEAEs leading to study drug interruption
- 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 by MedDRA System Organ Class (SOC) and Preferred Term (PT) using frequency counts and percentages (i.e., number and percentage of subjects with an event):

- All TEAEs
- Grade 3/4/5 TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Related TEAEs
- Serious TEAEs
- Related serious TEAEs
- TEAEs leading to death

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

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. Listings for SAEs and deaths will include a flag indicating the TEAE status.

9.4.1.1 Adverse Events of Special Interest

For this study, elevated transaminase events and rash events, as determined by MedDRA preferred terms in Appendix E, are considered as adverse events of special interest.

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

- Subjects with events
- Subjects with events by maximum severity
- Subjects with events leading to treatment discontinuation
- Subjects with events leading to treatment interruption

- Subjects with serious events
- Subjects with related serious events
- Subjects with events leading to death
- Duration of events
- Time-to-onset of first event

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

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

9.4.2 Clinical Laboratory

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

The number and percentage of subjects meeting at least 1 threshold analysis criterion, during the TE period will be summarized. The threshold analysis of shift from baseline will also be summarized for liver function tests (LFTs) laboratory parameters. The threshold analysis criteria are provided in Appendix F.

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

Results of urinalysis and positive urine/serum pregnancy test will be listed in individual subject data listings only. For positive serum pregnancy listing, subjects with serum HCG which are above non-pregnant levels will be selected.

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

[redacted]

[redacted]

9.4.6 Physical Examination

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

[redacted]

9.4.8 COVID-19 Impacted Visits

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

10 Interim and DMC Analyses

10.1 Interim Analysis

Not applicable.

10.2 DMC analysis

Not applicable.

11 REFERENCES

[1] Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall G, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.

[2] Kerem E, Wilschanski M, Miller NL, Pugatsch T, Cohen T, Blau H, Rivlin J, Shoseyov D, Reha A, Constantine S, Ajayi T. Ambulatory quantitative waking and sleeping cough assessment in patients with cystic fibrosis. Journal of Cystic Fibrosis. 2011 May 1;10(3):193-200.

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

[4] McLellan G, Arthur R, Donnelly S, Buchan DS. Segmented sedentary time and physical activity patterns throughout the week from wrist-worn ActiGraph GT3X+ accelerometers among children 7–12 years old. Journal of sport and health science. 2020 Mar 1;9(2):179-88.

12 LIST OF APPENDICES

Appendix A: Analysis Visit Windows for Safety and Efficacy Assessments

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

Assessment	Visit[1]	Target Study Day[2]	Analysis Visit Window (in study days)[3, 4, 5, 6]
Safety Assessment			
Serum Chemistry	Day 1 (Baseline) Week 13 Safety Follow-up	1 85 Not applicable	≤1 Pre-dose [57, 99] Use nominal visit
[redacted]			
BMI, Weight, Height and their Z-scores	Day 1 (Baseline) Week 13 Safety Follow-up	1 85 Not applicable	≤1 Pre-dose [57, 99] Use nominal visit
Efficacy Assessment			
Cough frequency[7]	Day -14 Day -7 Week 2 Week 3 Week 4 Week 5 Week 6 Week 7 Week 8 Week 9 Week 10 Week 11 Week 12	-14 -7 8 15 22 29 36 43 50 57 64 71 78	[-28, -8] Pre-dose [-7, 1] Pre-dose [1, 14] Post-dose [15, 21] [22, 28] [29, 35] [36, 42] [43, 49] [50, 56] [57, 63] [64, 70] [71, 77] [78, 92]
Step count [redacted]	Day -14 Day -7 Week 1 Week 2 Week 3 Week 4 Week 5 Week 6 Week 7 Week 8 Week 9 Week 10 Week 11 Week 12	Not applicable[2]	≤-8 (7-day window) [-7, -1] [1, 7] [8, 14] [15, 21] [22, 28] [29, 35] [36, 42] [43, 49] [50, 56] [57, 63] [64, 70] [71, 77] [78, 84]

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

[redacted]

Notes:
[1] Visit name for analysis purpose is used to report data in tables and figures. In this context, visit may not necessarily refer to a clinic visit and can include telemedicine contact or wearable device measurement.

[2] Step count and [redacted] are measured on a weekly basis, so this column denotes the first day of the 7-day interval.

[3] 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.

[4] For lab, ECG and vital sign 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.

[5] For safety assessments, the Safety Follow-up analysis visit will be based on the 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 > nominal Week 13 visit, then the ETT visit will be mapped into Safety Follow-up analysis visit.

[6] For nutrition variables (BMI, Weight, Height and their Z-scores), if there are multiple assessments > nominal Week 13 visit, then the nominal Safety Follow-up visit will be mapped to the Safety Follow-up visit. If there is only ETT assessment > nominal Week 13 visit, the ETT visit will be mapped to the Safety Follow-up visit; else if there are multiple assessments with > nominal Week 13 visit 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 (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 date.

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

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

   Obtain the age at informed consent (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 date.

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

Assessment	Visit[1]	Target Study Day[2]	Analysis Visit Window (in study days)[3, 4, 5, 6]

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

3. Missing first dose date or last dose date

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

   If the last dose date is missing or partial date is reported, the last dose date will be imputed based on, in descending order priority, the 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.

[redacted]

[7] The baseline value is defined as the geometric mean of valid cough measurements prior to the first dose of study drug (e.g., Day -14 and Day -7). If one value is missing or invalid, the non-missing, valid value will be used. If the cough frequency is zero at a given visit, 0.5 will be added to ensure a non-zero number.

[8] The baseline value will be defined as the average of valid weekly interval measurements prior to the first dose of study drug (e.g., average of Day -14 and Day -7). If one weekly interval measurement is missing or invalid, the non-missing, valid interval measurement will be used.

[9] The baseline value will be defined as the Day 1 assessment.

Appendix B: Details of GLI Equations for Calculating ppFEV$_1$

Percent predicted values will be calculated for parameters of FEV_1, FVC, FEV_1/FVC, and $FEF_{25\%-75\%}$ using the Quanjer GLI-2012 Regression Equations and Lookup Tables.

The regression equations and lookup tables required to implement the Quanjer GLI-2012 predicted values are available in:

Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Quanjer GLI-2012 Regression Equation and Lookup Tables (Version 7 April 2013). Global Lung Function Initiative. [online] Available at: http://www.ers-education.org/home/browse-all-content.aspx?idParent=138978 [Accessed Mar 26, 2018].

The instructions and tools on how to implement the Quanjer GLI-2012 equations are:

Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Implementing GLI-2012 regression equations (Version 19 July 2015). Global Lung Function Initiative. [online] Available at: http://www.ers-education.org/home/browse-all-content.aspx?idParent=138979 [Accessed Mar 26, 2018].

Sanja Stanojevic. GLI-2012 - SAS Macro (Version 2, 7 April 2013). Global Lung Function Initiative. [online] Available at: http://www.ers-education.org/home/browse-all-content.aspx?idParent=138988 [Accessed Mar 26, 2018].

Data handling rule for spirometry is as follows:

- Input age with at least 2 decimal place
- Use height at screening regardless if height is collected at other study visits for subjects whose age at informed consent is >21 years. For subjects with age <=21 years, height collected at the respective visit should be used; if the height at the respective visit is not available, the last non-missing record will be used.
- For race, map the CRF reported Black or African American to Black, all other races in CRF (except White) are mapped to 'other'; multiple checks for race in CRF are also mapped to 'other'; white is a reference race in the equations and assumes 0 values for all race coefficients in the GLI equations.

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

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

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date (in practical, use 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 (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 12-2 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 D: Imputation Rules for Missing AE dates

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

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

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

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

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

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

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

Imputation rules for partial AE end date are defined below:

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

Appendix E: Adverse Events of Special Interest

Table 12-7 MedDRA Preferred Terms for Event of Special Interest

Adverse event of special interest	MedDRA preferred terms
Elevated transaminase	Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Transaminases abnormal, Transaminases increased, Liver function test abnormal, Liver function test increased, Hypertransaminasaemia, Hepatic enzyme abnormal, Hepatic enzyme increased
Rash	Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash vesicular, Rash pruritic, Rash follicular, Rash pustular, Nodular rash, Drug eruption, Fixed eruption, Urticaria, Urticaria papular, Urticaria vesiculosa, Urticarial dermatitis, Rash morbilliform, Rash papular, Rash papulosquamous, Rash rubelliform, Rash scarlatiniform , Drug hypersensitivity, Type IV hypersensitivity reaction, Dermatitis, Dermatitis atopic, Epidermolysis, Skin toxicity, Dermatitis allergic, Dermatitis exfoliative, Dermatitis exfoliative generalised, Erythema multiforme, Exfoliative rash, Mucocutaneous rash, Acute generalised exanthematous pustulosis, Cutaneous vasculitis, Urticarial vasculitis, Dermatitis bullous, Drug reaction with eosinophilia and systemic symptoms, Epidermal necrosis, Oculomucocutaneous syndrome, Skin exfoliation, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, Perioral dermatitis, Vasculitic rash, Immune-mediated dermatitis, Penile rash, SJS-TEN overlap, Erythrodermic atopic dermatitis, Scrotal dermatitis

Note: the preferred terms listed in the table is based on the MedDRA version applicable at the time of finalization of the SAP. If the MedDRA version is upgraded at the time of the analysis, the corresponding preferred terms based on the upgraded version will be used in the analysis of adverse events of special interest.

Appendix F: Criteria for Threshold Analysis

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

Parameter	Threshold Analysis	Comments
Clinical Chemistry (LFT)		
ALT	>ULN - ≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >8x - ≤ 20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
AST	>ULN - ≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >8x - ≤ 20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
ALT or AST	(ALT>ULN - ≤ 3xULN) or (AST>ULN - ≤ 3xULN) (ALT>3x - ≤ 5xULN) or (AST>3x - ≤ 5xULN) (ALT>5x- ≤ 8xULN) or (AST>5x - ≤ 8xULN) (ALT>8x - ≤ 20xULN) or (AST>8x - ≤ 20xULN) ALT>20xULN or AST> 20 xULN	FDA DILI Guidance
Alkaline Phosphatase	>ULN - ≤ 1.5xULN >1.5 – ≤ 2.5 xULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>ULN - ≤ 1.5xULN >1.5 – ≤ 2xULN >2 – ≤ 3xULN >3 – ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
Direct Bilirubin	>ULN - ≤ 1.5xULN >1.5 – ≤ 2xULN >2 – ≤ 3xULN >3 – ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
Indirect Bilirubin	>ULN - ≤ 1.5xULN >1.5 – ≤ 2xULN >2 – ≤ 3xULN >3 – ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.

Table 12-3 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 >2.5 – ≤ 5.0xULN >5.0 – ≤ 20.0xULN >20.0xULN	CTCAE grade 1-4
Clinical Chemistry (NON-LFT)		
Albumin	<LLN - ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>1x - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Creatinine	>ULN - ≤ 1.5xULN >1.5 - ≤ 3.0xULN >3.0 - ≤ 6.0xULN >6.0xULN	CTCAE grades 1-4
Lipase	>ULN - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
Creatine kinase	>ULN - ≤ 2.5 x ULN >2.5 - ≤ 5 x ULN >5 - ≤ 10x ULN >10 x ULN	CTCAE grades 1-4

Table 12-4 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
HR	Bradycardia <50 bpm <45 bpm Decrease from baseline ≥10 bpm Decrease from baseline ≥20 bpm <50 bpm and decrease from baseline ≥10 bpm <50 bpm and decrease from baseline ≥20 bpm	Per HV grade 2, 3, plus shift change

Table 12-4 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
	Tachycardia >100 bpm >115 bpm >130 bpm Increase from baseline ≥10 bpm Increase from baseline ≥20 bpm >100 bpm and increase from baseline ≥10 bpm >100 bpm and increase from baseline ≥20 bpm	Per HV grade 1, 2, 3, plus shift change
PR	≥240 ms ≥300 ms ≥200 ms and increase from baseline ≥40 ms ≥200 ms and increase from baseline ≥100 ms	
QRS	>110 ms >160 ms Increase from baseline ≥20 ms Increase from baseline ≥40 ms	
QTc	>450 to <500ms (Male) or >470 to <500ms (Female) ≥500 ms Increase from baseline Increase from baseline >10 ms Increase from baseline >20 ms Increase from baseline >40 ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula.

Table 12-5 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
Pulse Rate	Same as above in ECG category	
SBP increased	>140 mmHg >160 mmHg >10 mmHg increase from baseline >20 mmHg increase from baseline >140 mmHg & >10 mmHg increase from baseline >140 mmHg & >20 mmHg increase from baseline >160 mmHg & >10 mmHg increase from baseline >160 mmHg & >20 mmHg increase from baseline	809/770 analyses

Table 12-5 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
SBP decrease	<90 mmHg <80 mmHg >10 mmHg decrease from baseline >20 mmHg decrease from baseline <90 mmHg and >10 mmHg decrease from baseline <90 mmHg and >20 mmHg decrease from baseline <80 mmHg and >10 mmHg decrease from baseline <80 mmHg and >20 mmHg decrease from baseline	Per HV grade 1, 3, plus shift change
DBP increased	>90 mmHg >100 mmHg >5 mmHg increase from baseline >10 mmHg increase from baseline >90 mmHg and >5 mmHg increase from baseline >90 mmHg and >10 mmHg increase from baseline >100 mmHg and >5 mmHg increase from baseline >100 mmHg and >10 mmHg increase from baseline	
DBP decreased	<60 mmHg <45 mmHg >5 mmHg decrease from baseline >10 mmHg decrease from baseline <60 mmHg and >5 mmHg decrease from baseline <60 mmHg and >10 mmHg decrease from baseline <45 mmHg and >5 mmHg decrease from baseline <45 mmHg and >10 mmHg decrease from baseline	
Weight	Weight gain ≥5 % increase from baseline ≥10 % increase from baseline ≥ 20% increase from baseline	CTCAE grade 1-3
	Weight loss ≥5 % decrease from baseline ≥10 % decrease from baseline ≥ 20% decrease from baseline	CTCAE grade 1-3

Table 12-6 Threshold Analysis Criteria for Laboratory Tests (for labeling purpose)

Parameter	Threshold Analysis	Comments
Clinical Chemistry (LFT)		
ALT or AST	>3xULN >5xULN >8xULN	For labeling purpose