VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX17-445-105 Version 5.0 and Protocol Number VX17-445-105 Version 5.4BE (Final Analysis)

A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous or Heterozygous for the *F508del* Mutation

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2.3 Modifications to the Approved DMC Charter

Not Applicable.

3 INTRODUCTION

This statistical analysis plan (SAP) for the final analysis of Study VX17-445-105 (Study 105) 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 and data presentations of safety and efficacy endpoints during Study 105 for subjects who previously participated in Study VX17-445-102 (Study 102), or Study VX17-445-103 (Study 103), and subsequently enrolled in Study 105. Four interim analyses (IA) were conducted (data cut date for IA1:10 July, 2019, data cut date for IA2: 31 October, 2019, data cut date for IA3: 25 March, 2021, and data cut for IA4: 28 March, 2022) for Study 105 after the datalock for the parent studies 102 and 103 based on SAP Version 1.0 for IA1 and IA2; SAP Version 2.0 for IA3; and SAP Version 4.0 for IA4.

The intent of the analysis proposed in this document is to conduct the final analysis when all subjects complete the study.

Due to the outbreak of COVID-19, to ensure continued safety of subjects who *cannot* travel to the study sites for their visits (for any reason due to COVID-19), specific alternative measures are being implemented to minimize the risk of exposure to COVID-19. The SAP Version 2.0, SAP Version 3.0, SAP Version 4.0, and SAP Version 5.0 summarize the additional statistical analyses that are related to these alternative measures.

The Vertex Biometrics Department will perform the statistical analysis described in this document; SAS (Version 9.4 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP Version 5.0 will be finalized and approved prior to the Study 105 final datalock date. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP.

4 OBJECTIVES FOR STUDY 105

4.1 Primary Objective (Treatment and Extension Period)

To evaluate the long-term safety and tolerability of elexacaftor (ELX; VX-445) in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects with CF who are homozygous or heterozygous for the *F508del* mutation

4.2 Secondary Objectives (Treatment Period Only)

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

5 ENDPOINTS FOR STUDY 105

5.1 Efficacy and Pharmacodynamic Endpoints (Treatment Period Only)

5.1.1 Primary Efficacy Endpoint

Not applicable

5.1.2 Secondary Efficacy and Pharmacodynamic Endpoints

- Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$)
- Absolute change in sweat chloride (SwCl)
- Number of pulmonary exacerbations (PEx)
- Time-to-first PEx
- Absolute change in body mass index (BMI)
- Absolute change in BMI z-score
- Absolute change in body weight
- Absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score

5.2 Safety Endpoints (Treatment and Extension Period)

- Adverse events (AEs)
- Clinical laboratory values
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry

5.3 Additional Endpoints (Treatment Period Only)

- Absolute change in CFQ-R non-respiratory domain scores
- Changes in inflammatory mediators
- Changes in microbiology analysis

6 DESIGN FOR STUDY 105

6.1 Overall Design

This is a Phase 3, multicenter, open-label study (OLS) for subjects who completed the last Treatment Period visit in a parent study and meet eligibility criteria. A schematic of the study design is shown in Figure 6-1.

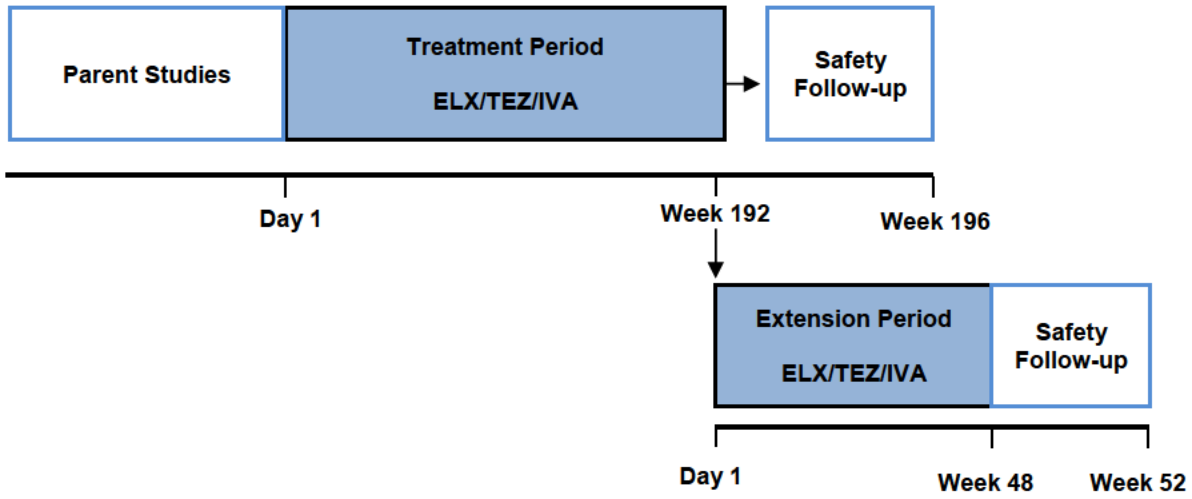
All subjects will receive a TC of ELX/TEZ/IVA at the same dose level as that evaluated in Study 102 and Study 103. Subjects who complete the Treatment Period will have the opportunity to participate in the Extension Period for an additional 48 weeks. The dosages for the Treatment and Extension Period are shown in Table 6-1.

Table 6-1 **ELX/TEZ/IVA** Dosages

ELX Dosage	TEZ Dosage	IVA Dosage
200 mg qd	100 mg qd	150 mg q12h

All visits will occur within the windows specified. Please refer to Table 3-1 of Study 105 CSP for details about the Treatment Period study visits and assessments and Table 3-2 for the Extension Period.

Figure 6-1 Schematic of the Study Design



ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor
Notes: Parent studies are Phase 3 Vertex studies investigating ELX/TEZ/IVA. These include VX17-445-102 (Study 102) and Study VX17-445-103 (Study 103). The timing of the Day 1 Visit in the Treatment Period and Extension Period Day 1 Visit is detailed in Section 9.1.1 in Study 105 CSP. Note that the figure is not drawn to scale.

For treatment continuity in countries where ELX/TEZ/IVA is not commercially available, an option to return to this study will be offered to subjects who depart the Extension Period to enroll in another Vertex study of investigational CFTR modulators (hereafter referred to as "another qualified Vertex study") based on the following:

- Subjects receive open-label ELX/TEZ/IVA during the other study's Run-in Period but do not qualify to receive study drug in the Treatment Period of the other study
- Meet all eligibility criteria for this study at their Returning Visit.

Subjects who resume participation in this study will resume treatment with study drug after completion of a Returning Visit. Resumption of participation in this study following departure to another qualified Vertex study will be permitted once.

6.2 Sample Size and Power

This is an open-label study that will enroll subjects from qualifying previous studies (Study 102 and 103) who meet the inclusion and exclusion criteria for this study. Over 400 subjects are expected to enroll in this open-label study of 196 weeks' duration. With this number of subjects exposed to ELX/TEZ/IVA treatment, AEs by Preferred Term (PT) that occur with a frequency of >1% will be ruled out with 95% confidence, when zero events are observed in that PT. Furthermore, with over 400 subjects exposed to ELX/TEZ/IVA treatment for at least 24 weeks, the half-width of the 95% CI for estimating the cumulative incidence of PEx is less than 6% assuming an observed incidence of 30%.

Approximately 30 subjects are expected to participate in the Extension Period.

6.3 Randomization

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

6.4 Blinding and Unblinding

Refer to the study 105 CSP section 10.7 for details.

6.5 Interim Analysis

Four interim analyses (IA) were conducted (data cut date for IA1:10 July 2019, data cut date for IA2: 31 October 2019, data cut date for IA3: 25 March 2021, and data cut for IA4: 28 March 2022) for Study 105 after the datalock of the parent studies 102 and 103 based on SAP Version 1.0 for IA1 and IA2; SAP Version 2.0 for IA3; and SAP Version 4.0 for IA4.

7 ANALYSIS SETS

The following analysis sets are defined: Open-label (OL) All Subjects Set, OL Extension Period All Subjects Set, OL Full Analysis Set, OL Safety Set, Cumulative Triple Combination (TC) Efficacy Set, and OL Extension Period Safety Set.

The OL All Subjects Set is defined as all subjects who were enrolled (defined as subject having data in the clinical database for the OLS) in the OLS Treatment Period. This analysis set will be used for Treatment Period individual subject data listings and disposition summary tables unless otherwise specified.

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

7.1 Efficacy Analysis Sets (Treatment Period only)

A summary of efficacy analysis sets is presented in Table 7-1.

Table 7-1 Summary of Efficacy Analysis Sets

Efficacy Set	Purpose	Studies	Treatment Label[§]
Study 102 FAS	To evaluate efficacy data during study 102	445-102	ELX/TEZ/IVA in 445-102 PBO in 445-102
Study 103 FAS	To evaluate efficacy data during study 103	445-103	ELX/TEZ/IVA in 445-103 TEZ/IVA in 445-103

OL Full Analysis Set (OL-FAS)	To evaluate efficacy data during study 105	445-105	ELX/TEZ/IVA in 445-102 PBO in 445-102 ELX/TEZ/IVA in 445-103 TEZ/IVA in 445-103 Any ELX/TEZ/IVA†
Cumulative TC Efficacy Set	To evaluate PEx data on ELX/TEZ/IVA during the parent study or during study 105	445-102 445-103 445-105	ELX/TEZ/IVA in 445-102 PBO in 445-102 Any ELX/TEZ/IVA

† does not apply for MMRM and descriptive summary of continuous efficacy endpoints
§ Treatment label is based on the treatment the subject was assigned to in the parent study. The "Any ELX/TEZ/IVA" group refers to all the subjects in the corresponding analysis set.

7.1.1 Parent Study Efficacy Analysis Set

The Parent Study Efficacy Analysis Sets are Study 102 Full Analysis Set (FAS) and Study 103 FAS. The definition of these analysis sets is same as the FAS definition in the SAP for Studies 102 and 103.

7.1.2 OL Full Analysis Set (OL-FAS)

The OL Full Analysis Set is defined as all enrolled subjects who received at least 1 dose of study drug in the OLS Treatment Period. The OL-FAS will be used for efficacy analysis in those subjects who had participated in Study 102, or Study 103 and then transitioned to the treatment cohort of Study 105. The efficacy data from subjects from the Parent Study 102 will be presented separately from the efficacy data for subjects from the Parent Study 103.

7.1.3 Cumulative TC Efficacy Set

The Cumulative TC Efficacy Set includes subjects who were randomized to ELX/TEZ/IVA and received at least one dose of study drug during the parent study and/or received at least one dose of study drug during the OLS Treatment Period. The Cumulative TC Efficacy Set will be used to analyze PEx data on ELX/TEZ/IVA during the parent study or during study 105 Treatment Period. PEx data for subjects from parent study 102 will be presented separately from the PEx data for subjects from parent study 103.

7.2 Safety Analysis Set

7.2.1 OL Safety Set (OL-SS)

The OL Safety Set is defined as all subjects who received at least 1 dose of study drug in the OLS Treatment Period. The OL-SS will be used primarily for safety analyses during OLS Treatment Period with the treatment label "Any ELX/TEZ/IVA".

7.2.2 OL Extension Period Safety Set (OL-EP-SS)

The **Open-label Extension Period Safety Set (OL-EP-SS)** is defined as all subjects who have received at least 1 dose of study drug in the Extension Period of the OLS. The OL-EP-SS will be used primarily for safety analyses during OLS Extension Period with the treatment label "Any ELX/TEZ/IVA".

8 ANALYSIS PERIOD

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

8.1 Parent Study Efficacy Period

The definition of this analysis period for subjects from study 102 is the same as the PEx analysis period defined in the SAP for study 102. For subjects from study 103, this will be same as the time from first dose of study drug in the treatment period of study 103 until the last efficacy assessment in study 103, which may be collected up to the Week 4 visit or the earlier of Day 29 and the completion of study participation if subject does not have the Week 4 visit. This analysis period will be used with the parent study efficacy analysis sets to analyze the efficacy data during the parent study.

8.2 Open Label (OL) Period

OL Efficacy Period: Time from the first dose of study drug in the OLS until the last efficacy assessment on or before Week 192 Visit, or the earlier of Day 1345 and the end of study participation if subject does not have the Week 192 Visit. This analysis period will be used with the OL-FAS to analyze efficacy data during the OLS for the final analysis.

OL Safety Period: The time from the first dose of study drug in the OLS to 28 days after the last dose date of the study drug in the OLS or to the completion date of study participation (Section 9.1.5 of the study 105 CSP), whichever occurs first. This analysis period will be used with the OL-SS to analyze the safety data during the OLS for the final analysis.

8.3 Cumulative TC Efficacy Period

For subjects who enrolled in the OLS, the time from the first dose of study drug in study 102 or study 103 (for subjects randomized to ELX/TEZ/IVA in these studies) or in study 105 (for subjects not randomized to ELX/TEZ/IVA in these studies) until the Week 192 Visit, or the earlier of Day 1345 and the end of study participation if subject does not have the Week 192 Visit. For subjects who did not enroll in the OLS and were randomized to ELX/TEZ/IVA in studies 102 or 103 and received study drug in the parent study, definition of this analysis period is the same as the parent study efficacy period. The cumulative TC Efficacy period for subjects from studies 102 and 103 who enrolled in the OLS is represented by the shaded portion in Figure 8-1. The cumulative TC Efficacy period will be used with the cumulative TC Efficacy set for analysis of PEx data. Note that the data between the Safety Follow-up Visit of the parent study and signing of OLS informed consent form will not be collected when there is a gap in time between these two milestones; the corresponding duration will be excluded from the cumulative TC Efficacy period.

Figure 8-1 Cumulative TC Efficacy Period for Subjects who enrolled in the OLS

Subjects from Study 102

ELX/TEZ/IVA	ELX/TEZ/IVA OLS

Placebo	ELX/TEZ/IVA OLS

Subjects from Study 103

TEZ/IVA Run-in	ELX/TEZ/IVA	ELX/TEZ/IVA OLS
TEZ/IVA Run-in	TEZ/IVA	ELX/TEZ/IVA OLS

8.4 OL Safety Extension Period

The time from the first dose of study drug in the Extension Period to 28 days after the last dose date of the study drug in the Extension Period or to the completion date of study participation, whichever occurs first. This analysis period will be used with the OL-EP-SS to analyze the safety data during the Extension Period for the Extension Period analysis.

9 STATISTICAL ANALYSIS

9.1 General Considerations

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

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, 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 value:

- The parent study baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the parent study (studies 102 or 103). The parent study baseline will be used to calculate the absolute and relative change from baseline for efficacy analyses unless otherwise specified.
- The TC safety baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the parent study (if the subject received at least one dose of ELX/TEZ/IVA during the parent study) or the first dose of study drug in the OLS (if the subject did not actually receive at least one dose of ELX/TEZ/IVA during the parent study). The TC safety baseline will be used in the safety analyses.

Change (absolute change) from baseline will be calculated as post-baseline value - baseline value.

The **Treatment-emergent (TE) Period** for the Treatment Period in the open-label study is the same as the OL safety period as described in section 8.2.
Unscheduled visits: Unscheduled visit measurements will be included in analyses 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, and maximum and minimum change from baseline values during the analysis period for the safety analyses
4) In individual subject data listings as appropriate

Visit windowing rules: The analysis visit windows for protocol-defined visits for study 105 are provided in Section 12.1. The visit window for the parent studies is described in the SAP for the individual parent studies.

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

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

Multiplicity: There will be no multiplicity adjustment, unless specified otherwise.

9.2 Background Characteristics

The analysis described in this section (except for study drug exposure) will be presented separately for subjects from parent studies 102 and 103.

9.2.1 Subject Disposition

A summary table of subject disposition in the OLS will be presented for the OL All Subjects Set by treatment group in the parent studies and overall, with the following categories:

- Enrolled (OL All Subjects Set)
- Dosed (OL-SS)
- Enrolled and dosed (OL-FAS)

The number and percentage (based on OL-FAS) of subjects in each of the following disposition categories will be summarized by treatment group in parent studies and overall:

- Completed Treatment
- Prematurely discontinued treatment and the reasons for discontinuation
- Completed study
- Prematurely discontinued the study and the reasons for discontinuation

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

9.2.2 Demographics and Baseline Characteristics

Demographics and parent study baseline characteristics will be summarized based on the OL-FAS, and presented by treatment group in parent studies and overall.

Demographic data will include the following:

- Age at parent study 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, Not Collected per Local Regulations and Other)
- Geographic region (North America, Europe [including Australia])

Parent study baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- BMI z-score (for subjects <=20 years old at parent study baseline)

Stratification categories (in addition to sex, if applicable) used in the parent study will include the following:

- Age at the Screening Visit of parent study (<18, and ≥18 years)
- $ppFEV_1$ determined during the Screening/Run-in Period of parent study (<70, and ≥70)

Note that one of the parent studies (study 103) had a 4-week TEZ/IVA run-in period during which the $ppFEV_1$ used in stratification was determined.

Disease characteristics based on parent study baseline will include the following:

- $ppFEV_1$ at parent study baseline (<40, ≥ 40 to <70, ≥70 to ≤90, and >90)
- $ppFEV_1$ at parent study baseline (continuous)
- Sweat chloride at parent study baseline (continuous)
- CFQ-R respiratory symptoms domain score at parent study 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 any bronchodilator (Yes, No)
- Prior use of any inhaled bronchodilator (Yes, No)
- Prior use of any inhaled hypertonic saline (Yes, No)
- Prior use of any inhaled corticosteroids (Yes, No)
- Infection with *Pseudomonas aeruginosa* within 2 years prior to screening visit (Positive, Negative) of parent study

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

No statistical tests will be carried out to evaluate any baseline imbalance between treatment groups.

9.2.3 Medical History

Medical history (referenced to the start of parent study) will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). For the OL-FAS, medical history will be summarized descriptively by treatment group in parent studies and overall and by System Organ Class (SOC) and Preferred Term (PT). The corresponding data listing will also be provided.

9.2.4 Prior and Concomitant Medications

Medications will be coded using the WHO-Drug Dictionary and categorized as follows:

- **Prior medication:** any medication that was administered during the 56 days before the first dose date of study drug in the OLS.
- **Concomitant medication:** medication continued or newly received during the OL safety period
- **Post-treatment medication:** medication continued or newly received after the OL safety 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 in the study 105 database has completely missing or partially missing start/stop date and if it cannot be determined whether it was taken before the first dose date of the OLS, concomitantly during the OL safety period, or after the OL safety 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 Section 12.2.

For the OL-FAS, prior medications and concomitant medications will be summarized descriptively by: 1) treatment group in parent studies and overall, Preferred Name (PN); and 2) treatment group in parent studies and overall, anatomic class (ATC) level 1, ATC level 2, and PN. Post-treatment medications will be listed for each subject.

9.2.5 Study Drug Exposure

Duration of study drug exposure is defined as [last dose date – first dose date + 1 day] within the OL safety period, regardless of any interruption in dosing between the first and the last dose. Study drug exposure (in weeks) during the OL safety period for the OL-SS will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized into the following categories: <=24 weeks, >24 to <=48 weeks, >48 to <=72 weeks, >72 to <=96 weeks, >96 to <=120 weeks, >120 to <=144 weeks, >144 to <=168 weeks, >168 to <=192 weeks, and >192 weeks. Additionally, the total study drug exposure, defined as the sum total of the study drug exposure across all subjects (in patient-weeks and patient-years), will be provided. The summary will be by "Any ELX/TEZ/IVA" group.

9.2.6 Study Drug Compliance

Study drug compliance for the OL efficacy period 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 on that day.

Percentage of study drug compliance will be summarized based on the OL-FAS and presented by treatment group in parent studies and overall. It will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max and summarized in categories (<80% vs. ≥80%) using frequency tables.

In addition, for the final analysis only, percentage of tablets taken during the OL efficacy period will be calculated using the following formula: 100 × [(total number of tablets dispensed) – (total number of tablets returned)] / (total number of tablets planned to be taken per day × duration of study drug exposure in days). A similar summary to those for the study drug compliance will be produced based on the OL-FAS.

9.2.7 Important Protocol Deviation

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. IPD rules will be developed and finalized prior to the clinical data lock for study 105.

The protocol deviations that should be considered as potential IPDs include, but are not limited to:

- Subject was enrolled in the study despite the violation of inclusion/exclusion criteria
- Subject received prohibited concomitant medications
- Subject received the wrong treatment or incorrect doses
- Subject remained in the study despite meeting withdrawal criteria

Occurrence of any of these events should be considered as potential IPDs, but a team should categorize them as IPDs only if they have the potential to significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

IPDs (from the site deviation log) during the OL Efficacy period will be summarized descriptively based on the OL-FAS and presented by treatment group in parent studies and overall. Additionally, IPDs during the OL Efficacy period will be provided in an individual subject data listing. IPDs will be analyzed only as part of final analysis.

9.2.8 Summary of Analysis of Background Characteristics

Background characteristics that will be analyzed for each analysis set is presented in Table 9-1.

Table 9-1 Analysis of Background Characteristics

Analysis Set	**Background characteristics**
OL All Subjects Set	Disposition
OL-FAS	Demographics (parent study baseline) Baseline characteristics (parent study baseline) Medical History Prior and Concomitant Medications Study drug compliance Important Protocol Deviation (final analysis only)
OL-SS	Study drug exposure

9.3 Efficacy Analysis

The parent study baseline will be used to calculate the change from baseline for continuous efficacy endpoints unless otherwise specified. The efficacy data from subjects with parent study 102 will be presented separately from those with parent study 103. Continuous endpoints during the parent study will be analyzed using the same mixed-effects model for repeated measures (MMRM) approach as described in the SAP for the parent study. The resulting estimates will be identical to what is available in the final CSR of the parent study. Similarly, continuous endpoints during the OL efficacy period will be analyzed using a separate MMRM. The descriptive summary for continuous endpoints and MMRM analysis during OL efficacy period will be restricted up to the Week 192 Visit.

The focus of the efficacy analysis will be on within-group comparison. No between-groups comparisons will be performed. *P* values will not be presented for any of the comparisons.

9.3.1 Analysis of Primary Efficacy Endpoint

Not applicable since efficacy is not a primary objective.

9.3.2 Analysis of Secondary Efficacy and Pharmacodynamic Endpoint

9.3.2.1 Definition of Variables

Percent predicted forced expiratory volume in 1 second ($ppFEV_1$): Percent predicted FEV_1 is the ratio of FEV_1 (L) and predicted FEV_1 (L), expressed as a percentage. See Section 12.6 for more details.

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

Pulmonary exacerbation (PEx): A PEx is defined as a new event or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the following signs/symptoms:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature above 38°C (equivalent to approximately 100.4°F)
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge

- Change in physical examination (PE) of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

The number of PEx is then defined as the total number of PEx for each treatment group during the cumulative TC Efficacy period.

The time to first PEx is the number of days from the start of the cumulative TC Efficacy period to the date of the first pulmonary exacerbation during the cumulative TC Efficacy period. A subject who does not experience a PEx during the cumulative TC Efficacy period will be censored at the cumulative TC Efficacy period end date.

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

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m}^2\text{)}}$$

BMI z-score: the BMI score, adjusted for age and sex, will be referred to as BMI-for-age z-score (BMI z-score). The BMI z-score will be calculated by using Centers for Disease Control and Prevention (CDC) growth charts[6], with the age (in months) used for the calculation defined in Section 12.1.

Cystic Fibrosis Questionnaire-Revised (CFQ-R): The CFQ-R[1,3,5] is a validated CF-specific instrument that measures quality-of-life domains. This study utilizes three different versions of CFQ-R:

- CFQ-R for Children ages 12 and 13
- CFQ-R for Adolescents and Adults (subjects 14 years and older)
- CFQ-R for Parents/Caregivers (subjects 13 years and younger)

In all three versions, specific question belonging to a domain is scored 1, 2, 3, or 4. The CFQ-R domain score, e.g., physical domain score or respiratory domain score, is defined as a scaled score as follows:

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

where the score from a negatively phrased question is first reversed, i.e., reversed score = 5 – actual score, so that 1 always represents the worst condition and 4 the best condition. The (scaled) domain score ranges from 0 (worst condition) to 100 (best condition). The scaled score for a specific domain will not be calculated if more than half of the questions in the domain have missing scores.

The (scaled) domain score from the CFQ-R for Children ages 12 and 13 and for Adolescent and Adults will be pooled within and across subjects for the analysis purpose.

9.3.2.2 Analysis Method

Absolute change from baseline in $ppFEV_1$

- Subjects in Study 102 FAS and the corresponding subjects in OL-FAS

The MMRM for the parent study efficacy period will be same as that described in the SAP for study 102. In the MMRM for the OL efficacy period, the absolute change from baseline in $ppFEV_1$ will be the dependent variable. The model will include treatment group (as randomized in parent study), visit, and treatment by visit interaction as fixed effects, with continuous baseline $ppFEV_1$ from parent study, age at screening of parent study (<18 versus ≥18 years of age) and sex (male versus female) as covariates.

The repeated-measures analysis will be based on the restricted maximum likelihood method assuming an unstructured covariance structure to model the within-subject errors. The denominator degrees of freedom will be based on the method proposed by Kenward-Roger[2]. If the model fails to converge due to the unstructured covariance assumption, a compound symmetry covariance structure will be used to model the within-subject errors. In the MMRM approach, assuming that the data are missing at random, no imputation of missing data will be performed.

Results from the 2 MMRMs will be presented in a single summary table. The number of subjects, least-squares means (LS means) for absolute change from baseline at scheduled visits within each treatment group along with the corresponding standard error (SE), and 95% confidence interval (CI) will be presented. The LS means (±SE) for absolute change from baseline at each visit will also be plotted by treatment groups.

In addition, the descriptive statistics for raw values and absolute changes from baseline in $ppFEV_1$ by treatment group and visit will be presented for the OL efficacy period in OL-FAS.

- Subjects in Study 103 FAS and the corresponding subjects in OL-FAS

The MMRM for the parent study efficacy period will be same as that described in the SAP for study 103. In the MMRM for OL efficacy period, the absolute change from baseline in $ppFEV_1$ will be the dependent variable. The model will include treatment group (as randomized in parent study), visit, and treatment by visit interaction as fixed effects, with continuous baseline $ppFEV_1$ from parent study, and age at screening of parent study (<18 versus ≥18 years of age) as covariates. Other details of the analysis and presentation of the results is similar to those for subjects from study 102.

Absolute change from baseline in SwCl

Analysis of this PD variable will be based on an MMRM similar to the analysis of the absolute change from baseline in $ppFEV_1$. Note that baseline $ppFEV_1$ from parent study will be retained as a covariate in the MMRM and baseline SwCl from parent study will not be included as a covariate. A descriptive summary of raw values and absolute changes from baseline will also be presented.

Number of PEx

- Cumulative TC Efficacy Set for subjects from study 102

The number of PEx during the cumulative TC efficacy period will be analyzed for subjects in the cumulative TC efficacy set using a negative binomial regression model and reported as event rate along with the 95% CI. The model will include treatment as a fixed effect and continuous baseline $ppFEV_1$ from parent study, age at screening of parent study (<18 versus ≥18 years of

age), and sex (male versus female) as covariates. The logarithm of the subject-specific cumulative TC efficacy period duration (in years; 1 year=48 weeks) will be treated as the offset in the model. If the model does not converge, the negative binomial regression model will be replaced with a Poisson regression model.

Similarly, the number of PEx (i) requiring hospitalization, and (ii) requiring IV antibiotic therapy will be analyzed.

- Cumulative TC Efficacy Set for subjects from study 103

The analysis of number of PEx during the cumulative TC efficacy period will be similar to that for subjects from study 102. The only exception is that sex will not be a covariate in the negative binomial model and the analysis will be based only on one treatment group ("Any ELX/TEZ/IVA"). The number of PEx requiring hospitalization as well as the number of PEx requiring IV antibiotic therapy will only be summarized descriptively by "Any ELX/TEZ/IVA" group; the descriptive summary will include number of subjects with PEx, sum of days (weeks) in cumulative TC efficacy period over all the subjects, the number of PEx, and the observed PEx rate.

Time to First PEx

The time to first PEx (in weeks) during the cumulative TC efficacy period will be analyzed based on the cumulative TC efficacy set (separately for subjects from study 102 and study 103). The Kaplan-Meier method will be used to produce a graphical presentation of the cumulative exacerbation-free rate and to estimate the cumulative exacerbation-free rate for the "Any ELX/TEZ/IVA" group for subjects from study 102 and study 103.

Absolute change from baseline in BMI

Analysis of this variable will be based on an MMRM similar to the analysis of the absolute change from baseline in $ppFEV_1$. Note that baseline $ppFEV_1$ from parent study will be retained as a covariate in the MMRM and baseline BMI from parent study will not be included as a covariate. The analysis will be conducted with the clinic assessed data only. An additional analysis may also be performed to include pooled data obtained in clinic and at home, if the home assessed data are reasonably consistent with the clinic assessed data. A descriptive summary of raw values and absolute changes from baseline will also be presented.

Absolute change from baseline in BMI Z-score (for subjects ≤20 years of age at parent study baseline)

Analysis of this variable will be based on an MMRM similar to the analysis of the absolute change from baseline in $ppFEV_1$ (except that age at screening of parent study will not be a covariate). Note that baseline $ppFEV_1$ from parent study will be retained as a covariate in the MMRM and baseline BMI Z-score from parent study will not be included as a covariate. The analysis will be conducted with the clinic assessed data only. An additional analysis may also be performed to include pooled data obtained in clinic and at home, if the home assessed data are reasonably consistent with the clinic assessed data. A descriptive summary of raw values and absolute changes from baseline will also be presented.

Absolute change from baseline in body weight

Analysis of this variable will be based on an MMRM similar to the analysis of the absolute change from baseline in $ppFEV_1$. Note that baseline $ppFEV_1$ from parent study will be retained

as a covariate in the MMRM and baseline weight from parent study will not be included as a covariate. The analysis will be conducted with the clinic assessed data only. An additional analysis may also be performed to include pooled data obtained in clinic and at home, if the home assessed data are reasonably consistent with the clinic assessed data. A descriptive summary of raw values and absolute changes from baseline will also be presented.

Absolute change from baseline in CFQ-R respiratory domain score

Analysis of this variable will be based on an MMRM similar to the analysis of the absolute change from baseline in $ppFEV_1$. Note that baseline $ppFEV_1$ from parent study will be retained as a covariate in the MMRM and baseline CFQ-R respiratory domain score from parent study will not be included as a covariate. The analysis will include pooled CFQ-R RD score assessed at clinic and at home. An additional analysis may be performed to include only the clinic assessed CFQ-R RD score, if the home assessed data are inconsistent with the clinic assessed data. A descriptive summary of raw values and absolute changes from baseline will also be presented.

9.3.2.3 Sensitivity and Supportive Analysis of Secondary Endpoints

No sensitivity or supportive analysis is planned for the secondary endpoints.

9.3.2.4 Subgroup Analysis

No subgroup analysis is planned for the secondary endpoint.

9.3.3 Analysis of Additional Efficacy Variables

9.3.3.1 Additional Spirometry Variables

Summary statistics for raw values and for changes from parent study baseline of the following spirometry measurements during the OL efficacy period within OL-FAS will be presented at each visit:

- FEV_1:
  - Absolute change from parent study baseline in FEV_1 (L)
  - Relative change from parent study baseline in FEV_1 (%)
  - Relative change from parent study baseline in percent predicted FEV_1 (%)
- FVC:
  - Absolute change from parent study baseline in FVC (L)
  - Relative change from parent study baseline in FVC (%)
  - Absolute change from parent study baseline in percent predicted FVC (percentage points)
  - Relative change from parent study baseline in percent predicted FVC (%)
- $FEF_{25-75\%}$:
  - Absolute change from parent study baseline in $FEF_{25-75\%}$ (L/sec)
  - Relative change from parent study baseline in $FEF_{25-75\%}$ (%)
  - Absolute change from parent study baseline in percent predicted $FEF_{25-75\%}$ (percentage points)

- Relative change from parent study baseline in percent predicted $FEF_{25-75\%}$ (%)

- FEV_1/FVC:
  - Absolute change from parent study baseline in FEV_1/FVC
  - Relative change from parent study baseline in FEV_1/FVC (%)
  - Absolute change from parent study baseline in percent predicted FEV_1 / FVC
  - Relative change from parent study baseline in percent predicted FEV_1 / FVC (%)

9.3.4 Summary of Efficacy Analysis

Efficacy endpoint analysis for each efficacy analysis set is presented in Table 9-2.

Table 9-2 Summary of Efficacy Analysis

Analysis Set (Analysis description)	Efficacy Endpoint
Study 102 FAS and Study 103 FAS (MMRM) Note: Analysis is the same as what is specified in the SAP for studies 102 and 103	• Absolute change from baseline in $ppFEV_1$ • Absolute change from baseline in SwCl (PD endpoint) • Absolute change from baseline in BMI • Absolute change from baseline in BMI Z-score • Absolute change from baseline in weight • Absolute change from baseline in CFQ-R respiratory domain
OL-FAS (MMRM and descriptive summary; separately for subjects from study 102 and 103)	• Absolute change from baseline in $ppFEV_1$ • Absolute change from baseline in SwCl • Absolute change from baseline in BMI • Absolute change from baseline in BMI Z-score • Absolute change from baseline in weight • Absolute change from baseline in CFQ-R respiratory domain • Additional spirometry (descriptive summary only)
Cumulative TC Efficacy Set (Negative Binomial regression for counts, Kaplan-Meier for time to first PEx; separately for subjects from study 102 and 103)	• Number of PEx • Number of PEx requiring hospitalization (only descriptive for subjects from study 103) • Number of PEx requiring IV antibiotic therapy (only descriptive for subjects from study 103) • Time to First PEx

Note: baseline used is parent study baseline

9.4 Safety Analysis

The primary objective of study 105 is the evaluation of the long-term safety and tolerability of ELX/TEZ/IVA. All safety analyses for study 105 will be based on the OL safety period for subjects in the OL-SS.

The following safety and tolerability endpoints will be assessed:

- Treatment-emergent adverse events (TEAEs)

- Clinical laboratory values
- ECGs
- Vital signs
- Pulse oximetry

The safety analysis will be performed by pooling the safety data from patients with parent studies 102 and 103.

The TC safety baseline will be used to calculate change from baseline for continuous safety endpoints.

In the AE summary tables, AE data from the OLS safety period may be displayed side-by-side with the AE data from study 102.

Only descriptive analysis of safety will be performed. No statistical testing will be performed.

9.4.1 Adverse Events

AEs will be classified as pretreatment AEs, TEAEs, or post-treatment AEs, defined as follows:

Pretreatment AE**:** any AE that occurred prior to the start of the OL safety period

TEAE**:** any AE that worsened (either in severity or seriousness) or newly developed during the OL safety period

Post-treatment AE**:** any AE that worsened (either in severity or seriousness) or that was newly developed after the OL safety period

For AEs in the study 105 database with completely missing or partially missing start dates, if there is no clear evidence that the AEs started before the OL safety period or after the OL safety period, the AEs will be classified as TEAEs.

Details for imputing missing or partial start dates of adverse events are described in Section 12.3.

An overview of all TEAEs during OL safety period will be summarized and include 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
- Subjects with TEAEs leading to study drug interruption
- Subjects with Grade 3/4 TEAEs
- Subjects with related TEAEs
- Subjects with serious TEAEs
- Subjects with related serious TEAEs

- Subjects with TEAE leading to death

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

The following summary tables of TEAEs during OL safety period will be presented:

- All TEAEs
- Grade 3/4 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) and the exposure adjusted event rate (except for summary by strongest relationship and maximum severity). When summarizing the number and percentages of subjects, subjects with multiple occurrences of the same adverse event will be counted once, and only the maximum severity level will be presented in the severity summaries, and the strongest relationship level in the relationship summaries. Missing severity levels will not be included in the Grade 3/4 TEAE summaries; missing relationship will be considered as related and included in the related TEAE and related serious TEAE summaries.

Additional summary table in which the frequency counts and percentages as well as the exposure adjusted event rate will be presented for TEAEs during the OL safety period:

- All TEAEs by PT

All AEs in study 105 database, including pretreatment AEs, TEAEs, and post-treatment AEs, will be presented in an individual subject data listing based on the OL All Subjects Set. In addition, a listing containing individual subject adverse event data for TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, Grade 3/4 TEAEs, SAEs and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.

9.4.2 Clinical Laboratory Assessments

For the laboratory assessments during OL safety period, the observed values and change from TC safety 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 during the OL safety period will be summarized. The threshold analysis criterion shift from TC safety baseline will also be summarized for selected laboratory parameters. The threshold analysis criteria are provided in Section 12.4.

Results of positive urine/serum pregnancy test from study 105 will be presented in individual subject data listings only. For positive serum pregnancy listing, subjects with serum HCG which are abnormally high will be selected. In addition, a listing containing individual subject hematology, chemistry, and coagulation values from study 105 will be provided. This listing will include data from both scheduled and unscheduled visits. The listings will be based on OL All Subjects set.

9.4.3 Electrocardiogram

For the following ECG interval measurements during the OL safety period, a summary of observed values and change from TC safety baseline values will be provided at each visit (in msec): RR, PR, QT, and QT corrected for HR (QTcF), QRS duration, and HR (beats per minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion event during the OL safety period will be summarized. The threshold analysis criteria are provided in Section 12.4.

9.4.4 Vital Signs

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

The number and percentage of subjects meeting at least 1 threshold analysis criterion event during the OL safety period will be summarized. The threshold analysis criteria are provided in Section 12.4.

9.4.5 Pulse Oximetry

For the percent of oxygen saturation measurements using pulse oximetry during the OL safety period, a summary of observed values and change from TC safety baseline values will be provided at each visit.

The number and percentage of subjects with shift changes from TC safety baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the OL safety period will be summarized.

9.4.6 Physical Examination

No tables/figures/listings will be provided for physical examination data.

9.4.7 Ophthalmologic Examination

Ophthalmologic examination results for OL All Subjects Set will be provided in a data listing.

9.4.8 COVID-19 Impacted Visits

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

9.4.9 Safety Supportive Analysis

Elevated transaminases events and rash events, as determined by MedDRA PTs in Section 12.5, are considered as adverse events of special interest. The corresponding AE data will be summarized in terms of frequency counts and exposure adjusted rates.

9.4.9.1 Adverse Events of Special Interest

For treatment-emergent elevated transaminases events and rash events corresponding to the OL safety period, the following categories will be summarized:

- Subjects with events
- Subjects with events by maximum severity
- Subjects with events leading to treatment discontinuation
- Subjects with events leading to treatment interruption
- Subjects with serious events
- Subjects with related serious events
- Subjects with events leading to death
- Duration of events
- Time-to-onset of first event (with the first dose date of study drug in the OLS as the reference while calculating time-to-onset)

Note that for maximum severity, duration of events and time to onset of first event, the exposure adjusted rates will not be presented.

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

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

9.4.10 Summary of Safety Analysis

Safety assessments for each safety analysis set is presented in Table 9-3.

Table 9-3 Summary of Safety Analysis

Analysis Set	Safety Assessment
OL-SS	• AEs, SAEs, Grade 3/4 AEs, AEs leading to discontinuation or interruption, related AEs and SAEs, overview (corresponding exposure adjusted rates) • Clinical laboratory (Summary of change from TC safety baseline, TA including shift from TC safety baseline) • Vital signs (Summary of change from TC safety baseline, TA)

	• ECG (Summary of change from TC safety baseline, TA) • Pulse oximetry (Summary of change from TC safety baseline, Shift from TC safety baseline) • Ophthalmologic examination (listing) Special safety topics (includes exposure adjusted rates): • Rash (including by subgroup: sex, hormonal therapy) • Elevated transaminases events

9.5 Additional Analysis

Analyses related to the additional endpoints of changes in inflammatory mediators, changes in microbiology analysis and rate of change in ppFEV$_1$ will be discussed in a separate document.

9.5.1 Analysis of absolute change from baseline in CFQ-R non-respiratory domain score

Analysis of these domains will be based on an MMRM similar to the analysis of the absolute change from baseline in ppFEV$_1$. The mean plot will not be produced for these domains.

9.6 Extension Period

Unless otherwise specified, statistical analyses for Study 105 Extension Period will be similar to the analyses previously documented in Sections 9.1, 9.2, and 9.4.

9.6.1 General Considerations

Baseline value: The Extension Period TC safety baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the parent study (if the subject received at least one dose of ELX/TEZ/IVA during the parent study) or the first dose of study drug in the Treatment Period (if the subject did not receive at least one dose of ELX/TEZ/IVA during the parent study). The Extension Period TC safety baseline will be used in the safety analyses for the Extension Period.

The **Treatment-emergent (TE) Period** in the Extension Period is the same as the OL Safety Extension Period described in Section 8.4.

9.6.2 Background Characteristics

9.6.2.1 Subject Disposition

A summary table of subject disposition in the Extension Period will be presented for the OL Extension Period All Subjects Set with the following categories:

- Enrolled (OL Extension Period All Subjects Set)
- Dosed (OL-EP-SS)

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

- Completed Treatment in the Extension Period
- Prematurely discontinued treatment in the Extension Period and the reasons for discontinuation

- Completed Extension Period study
- Prematurely discontinued the Extension Period study and the reasons for discontinuation

A listing will be provided for subjects who discontinued treatment during Extension Period or who discontinued Extension Period with reasons for discontinuation.

9.6.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized based on the OL-EP-SS.

Demographic data will include the following:

- Age at parent study 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, Not Collected per Local Regulations and Other)

Baseline characteristics based on parent study baseline will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- BMI z-score (for subjects <=20 years old at parent study baseline)

Disease characteristics based on parent study baseline will include the following:

- $ppFEV_1$ at parent study baseline (<40, ≥ 40 to <70, ≥70 to ≤90, and >90)
- $ppFEV_1$ at parent study baseline (continuous)
- Sweat chloride at parent study baseline (continuous)
- CFQ-R respiratory symptoms domain score at parent study baseline (continuous)

9.6.2.3 Medical History

Medical history (referenced to the start of parent study) will be coded by using MedDRA. A listing with System Organ Class (SOC) and Preferred Term (PT) will be provided.

9.6.2.4 Prior and Concomitant Medications

Medications will be coded using the WHO-Drug Dictionary and categorized as follows:

- **Prior medication:** any medication that was administered during the 56 days before the first dose date of study drug in the Extension Period.
- **Concomitant medication:** medication continued or newly received during the OL Safety Extension Period.
- **Post-treatment medication:** medication continued or newly received after the OL Safety Extension 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 in the study 105 Extension Period database has completely missing or partially missing start/stop date and if it cannot be determined whether it was taken before the first dose date of the Extension Period, concomitantly during the OL Safety Extension Period, or after the OL Safety Extension 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 Section 12.2.

A listing will be provided.

9.6.2.5 Study Drug Exposure

Duration of study drug exposure is defined as [last dose date – first dose date + 1 day] within the OL Safety Extension Period, regardless of any interruption in dosing between the first and the last dose. Study drug exposure (in weeks) during the OL Safety Extension Period for the OL-EP-SS will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized into the following categories: <=24 weeks, >24 to <=48 weeks, >48 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) in the Extension Period, will be provided. The summary will be by "Any ELX/TEZ/IVA" group.

9.6.2.6 Study Drug Compliance

Study drug compliance for the OL Extension Period 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 on that day. A listing of the compliance rate will be provided.

9.6.2.7 Important Protocol Deviation

IPD for the Extension Period is similarly defined but for the OL Extension Period.

IPDs (from the site deviation log) during the OL Extension Period will be provided in an individual subject data listing.

9.6.3 Safety Analysis

The primary objective of study 105 Extension Period is the evaluation of the long-term safety and tolerability of ELX/TEZ/IVA. All safety analyses for study 105 Extension Period will be based on the OL Extension Period for subjects in the OL-EP-SS.

The following safety and tolerability endpoints will be assessed:

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

In the AE summary tables, AE data from the OL Safety Extension Period may be displayed side-by-side with the AE data from study 102.

Only descriptive analysis of safety will be performed. No statistical testing will be performed.

9.6.3.1 Adverse Events

AEs will be classified as pretreatment AEs, TEAEs, or post-treatment AEs, defined as follows:

Pretreatment AE**:** any AE that occurred prior to the start of the OL Safety Extension Period.

TEAE**:** any AE that worsened (either in severity or seriousness) or newly developed during the OL Safety Extension Period

Post-treatment AE**:** any AE that worsened (either in severity or seriousness) or that was newly developed after the OL Safety Extension Period

For AEs in the study 105 Extension Period database with completely missing or partially missing start dates, if there is no clear evidence that the AEs started before the OL Safety Extension Period or after the OL Safety Extension Period, the AEs will be classified as TEAEs.

Details for imputing missing or partial start dates of adverse events are described in Section 12.3.

An overview of all TEAEs during OL Safety Extension Period will be summarized and include 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
- Subjects with TEAEs leading to study drug interruption
- Subjects with Grade 3/4 TEAEs
- Subjects with related TEAEs
- Subjects with serious TEAEs
- Subjects with related serious TEAEs
- Subjects with TEAE leading to death

The following summary tables of TEAEs will be presented for overall:

- All TEAEs
- All TEAEs by PT

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 percentages of subjects, subjects with multiple occurrences of the same adverse event or a continuing adverse event will be counted once.

All AEs, including pre-treatment AEs, TEAEs, and post-treatment AEs, will be presented in an individual subject data listing based on the OL Extension Period All Subjects Set. In addition, separate listings containing individual subject adverse event data for TEAEs leading to treatment discontinuation, and SAEs will be provided, with a flag indicating the TEAE status for SAEs.

9.6.3.2 Clinical Laboratory Assessments

The number and percentage of subjects meeting at least 1 threshold analysis criterion event during the OL Extension Period will be summarized. The threshold analysis criterion shift from TC safety baseline will also be summarized for selected laboratory parameters. The threshold analysis criteria are provided in Section 12.4.

Results of positive urine/serum pregnancy test from study 105 Extension Period will be presented in individual subject data listings only. For positive serum pregnancy listing, subjects with serum HCG which are abnormally high will be selected. In addition, a listing containing individual subject hematology, chemistry, and coagulation values from study 105 Extension Period will be provided. This listing will include data from both scheduled and unscheduled visits. The listings will be based on OL Extension Period All Subjects set.

9.6.3.3 Electrocardiogram

The number and percentage of subjects meeting at least 1 threshold analysis criterion event during the OL Extension Period will be summarized. The threshold analysis criteria are provided in Section 12.4. A listing containing the RR, PR, QT, and QT corrected for HR (QTcF), QRS duration, and HR (beats per minute) measurements during the OL Extension Period will be provided.

9.6.3.4 Vital Signs

The number and percentage of subjects meeting at least 1 threshold analysis criterion event during the OL Extension Period will be summarized. The threshold analysis criteria are provided in Section 12.4. A listing containing the systolic and diastolic blood pressure (mm Hg), weight (kg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute) measurements during the OL Extension Period will be provided.

9.6.3.5 Pulse Oximetry

A listing containing the percent of oxygen saturation measurements during the OL Extension Period will be provided.

9.6.3.6 Physical Examination

No tables/figures/listings will be provided for PE data during the OL Extension Period.

9.6.3.7 Ophthalmologic Examination

Ophthalmologic examination results for OL Extension Period All Subjects Set will be provided in a data listing.

9.6.3.8 COVID-19 Impacted Visits

A listing containing subjects' visits impacted due to COVID-19 during the OL Extension Period will be provided.

10 Interim and DMC Analysis for Study 105

10.1 Interim Analysis

Per the CSP, IAs for Study 105 may have taken place at any time during the study at the discretion of the sponsor to support regulatory and/or reimbursement dossiers. IA1 was conducted after the data lock of parent Studies 102 and 103 under SAP Version 1.0. As of November 2022, 3 additional IAs were conducted: IA2 (under SAP Version 1.0), IA3 (SAP Version 2.0), and IA4 (SAP Version 4.0). The analysis details of the IAs can be found in their respective SAP versions.

10.2 DMC Analysis

An independent data monitoring committee (IDMC) was formed before initiation of study 105. The IDMC's objectives and operational details are described in the IDMC charter. The IDMC will conduct regular planned safety reviews of study data as outlined in the IDMC Charter and IDMC Analysis Plan.

11 REFERENCES

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12 APPENDICES

12.1 Analysis Visit Windows for Efficacy and Safety Assessments (Treatment Period Only)

Table 12-1 Analysis Visit Windows for Efficacy and Safety Assessments in Study 105

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2]
Serum Chemistry Hematology Vital Signs[3]	TC Safety baseline	--	Defined in Section 9.1
	OL Day 15	15	[1, 22] where day 1 is post-dose measurement
	OL Week 4	29	(22, 43]
	OL Week 8	57	(43, 85]
	OL Week 16	113	(85, 141]
	OL Week 24	169	(141, 211]
	OL Week 36	253	(211, 295]
	OL Week 48	337	(295, 379]
	OL Week 60	421	(379, 463]
	OL Week 72	505	(463, 547]
	OL Week 84	589	(547, 631]
	OL Week 96	673	(631, 715]
	OL Week 108	757	(715, 799]
	OL Week 120	841	(799, 883]
	OL Week 132	925	(883, 967]
	OL Week 144	1009	(967, 1051]
	OL Week 156	1093	(1051, 1135]
	OL Week 168	1177	(1135, 1219]
	OL Week 180	1261	(1219, 1303]
	OL Week 192	1345	(1303, 1359]
	OL Safety Follow-up	Not applicable	Use nominal visit
Standard 12-lead ECG	TC Safety baseline	--	Defined in Section 9.1
	OL Day 15	15	[1, 36] where day 1 is post-dose measurement
	OL Week 8	57	(36, 113]
	OL Week 24	169	(113, 253]
	OL Week 48	337	(253, 421]
	OL Week 72	505	(421, 589]
	OL Week 96	673	(589, 757]
	OL Week 120	841	(757, 925]
	OL Week 144	1009	(925, 1093]
	OL Week 168	1177	(1093, 1261]
	OL Week 192	1345	(1261, 1359]
	OL Safety Follow-up	Not applicable	Use nominal visit

Table 12-1 Analysis Visit Windows for Efficacy and Safety Assessments in Study 105

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2]
Coagulation	TC Safety baseline	--	Defined in Section 9.1
	OL Week 24	169	[1, 253] where day 1 is post-dose measurement
	OL Week 48	337	(253, 421]
	OL Week 72	505	(421, 589]
	OL Week 96	673	(589, 757]
	OL Week 120	841	(757, 925]
	OL Week 144	1009	(925, 1093]
	OL Week 168	1177	(1093, 1261]
	OL Week 192	1345	(1261, 1359]
	OL Safety Follow-up	Not applicable	Use nominal visit
Spirometry	Parent Study baseline	--	≤1 corresponding to the first dose date of parent study
	OL Day 15	15	(1, 22]
	OL Week 4	29	(22, 43]
	OL Week 8	57	(43, 85]
	OL Week 16	113	(85, 141]
	OL Week 24	169	(141, 211]
	OL Week 36	253	(211, 295]
	OL Week 48	337	(295, 379]
	OL Week 60	421	(379, 463]
	OL Week 72	505	(463, 547]
	OL Week 84	589	(547, 631]
	OL Week 96	673	(631, 715]
	OL Week 108	757	(715, 799]
	OL Week 120	841	(799, 883]
	OL Week 132	925	(883, 967]
	OL Week 144	1009	(967, 1051]
	OL Week 156	1093	(1051, 1135]
	OL Week 168	1177	(1135, 1219]
	OL Week 180	1261	(1219, 1303]
	OL Week 192	1345	(1303, 1401]
	OL Safety Follow-up	Not applicable	Use nominal visit
CFQ-R	Parent Study baseline	--	≤1 corresponding to the first dose date of parent study
	OL Week 4	29	(1, 43]
	OL Week 8	57	(43, 113]
	OL Week 24	169	(113, 253]
	OL Week 48	337	(253, 421]
	OL Week 72	505	(421, 589]
	OL Week 96	673	(589, 757]
	OL Week 120	841	(757, 925]
	OL Week 144	1009	(925, 1093]
	OL Week 168	1177	(1093, 1261]
	OL Week 192	1345	(1261, 1401]
	OL Safety Follow-up	Not applicable	Use nominal visit

Table 12-1 Analysis Visit Windows for Efficacy and Safety Assessments in Study 105

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2]
Weight, Height and BMI (and the corresponding z-score)[4]	Parent Study baseline	--	≤1 corresponding to the first dose date of parent study
	OL Day 15	15	(1, 22]
	OL Week 4	29	(22, 43]
	OL Week 8	57	(43, 85]
	OL Week 16	113	(85, 141]
	OL Week 24	169	(141, 211]
	OL Week 36	253	(211, 295]
	OL Week 48	337	(295, 379]
	OL Week 60	421	(379, 463]
	OL Week 72	505	(463, 547]
	OL Week 84	589	(547, 631]
	OL Week 96	673	(631, 715]
	OL Week 108	757	(715, 799]
	OL Week 120	841	(799, 883]
	OL Week 132	925	(883, 967]
	OL Week 144	1009	(967, 1051]
	OL Week 156	1093	(1051, 1135]
	OL Week 168	1177	(1135, 1219]
	OL Week 180	1261	(1219, 1303]
	OL Week 192	1345	(1303, 1401]
	OL Safety Follow-up	Not applicable	Use nominal visit
SwCl	Parent study baseline	--	≤1 corresponding to the first dose date of parent study
	OL Day 15	15	(1, 22]
	OL Week 4	29	(22, 43]
	OL Week 8	57	(43, 85]
	OL Week 16	113	(85, 141]
	OL Week 24	169	(141, 337]
	OL Week 72	505	(337, 589]
	OL Week 96	673	(589, 757]
	OL Week 120	841	(757, 925]
	OL Week 144	1009	(925, 1093]
	OL Week 168	1177	(1093, 1261]
	OL Week 192	1345	(1261, 1401]

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:
1. If no numerical measurement is available within a visit window, the measurement will be considered missing for the visit.
2. 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.

Table 12-1 Analysis Visit Windows for Efficacy and Safety Assessments in Study 105

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2]

[3] For unscheduled vital signs measurements collected at Study Day 1, if any, they will be treated as post-dose observations.

[4] Weight will also be used in the threshold analysis in which the TC safety baseline will be used to calculate change.

Derived Variables:

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

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

   Obtain the informed consent date.

   Then age (in years) at first dose or post-baseline visit = [(first dose date or post-baseline visit date – informed consent date in parent study) in days + age at informed consent (in days) in parent study]/365.25.

2. Age (in months) at first dose date and post-baseline visit (for use in calculation of BMI and weight z-score):

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

   Obtain the informed consent date.

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

3. Missing first dose date or last dose date

   If the 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. Electrocardiogram:

   TC safety Baseline is defined in Section 9.1. If multiple ECG measurements are obtained on the same calendar day during the analysis period,
   - For summary purpose, the average value will be used as the ECG on that day;
   - For threshold analysis purpose, all ECG values will be used

12.2 Imputation Rules for Missing Prior/Concomitant Medication Dates

Imputation rules for missing or partial medication start/stop dates in study 105 database 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 (for programming purpose use Jan. 01, 2000 to impute).
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last day of the month.
    b. If DAY and Month are both missing, use the last day of the year.
    c. If DAY, Month and year are all missing, assign 'continuing' status to stop date (for programming purpose use Dec. 31, 2050 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

Same imputation rule will be implemented for missing and/or partial dates of non-pharmacological treatment/procedure.

12.3 Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date in study 105 database are defined below. If the imputed AE start date is before the informed consent date for the Treatment Period (Extension Period) OLS, the AE start date will be imputed using the informed consent date (Extension Period enrollment date). Ongoing events from the parent studies will follow the imputation rule described in the SAP for parent studies.

- **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 (Extension Period) OLS 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 (Extension Period) OLS, then impute the AE start day as the day of first dose date of the Treatment Period (Extension Period) OLS;
        - 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 (Extension Period) OLS or AE end date is missing, then
        - if AE start year is equal to the year of first dose date of the Treatment Period (Extension Period) OLS, then impute the AE start month and day as the month and day of first dose date of the Treatment Period (Extension Period) OLS;
        - else impute the AE start month as January and day as 1.
    - else impute the AE start month as January and day as 1.

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

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

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

Imputation rules for partial AE end date in study 105 database are defined below:

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

12.4 Criteria for Threshold Analysis

Table 12-3 Threshold Analysis Criteria for Laboratory Tests

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

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 - ≤ 2.5xULN >2.5 - ≤ 5xULN >5 - ≤ 10xULN >10xULN	CTCAE grades 1-4
Hematology		
Hemoglobin	Hgb decreased (anemia) <LLN - ≥ 100 g/L <100 – ≥ 80 g/L < 80 g/L	CTCAE grade 1-3
	Hgb increased >ULN - ≤ 20 g/L above ULN >20 g/L above ULN - ≤ 40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3

Table 12-3 Threshold Analysis Criteria for Laboratory Tests

Parameter	Threshold Analysis	Comments
Platelets	Platelet decreased <LLN - ≥ 75.0 x 10e9 /L <75.0 – ≥ 50.0 x 10e9 /L <50.0 – ≥ 25.0 x 10e9 /L <25.0 x 10e9 /L	CTCAE grade 1-4
	Platelet increased >ULN	No CTCAE available
Reticulocytes/Erythrocytes (%)	<LLN >ULN	No CTCAE
Coagulation		
Activated partial thromboplastin time (PTT)	>ULN - ≤ 1.5xULN >1.5 – ≤ 2.5xULN >2.5xULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤ 1.5xULN >1.5 – ≤ 2.5xULN >2.5xULN	CTCAE grade 1-3

Table 12-4 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

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

Parameter	Threshold Analysis	Comments
	Tachycardia	Per HV grade 1, 2, 3, plus shift change
	>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	
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)	To be applied to any kind of QT correction formula.
	≥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	

Note: Based on CPMP 1997 guideline.

Table 12-6 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 and >10 mmHg increase from baseline >140 mmHg and >20 mmHg increase from baseline >160 mmHg and >10 mmHg increase from baseline >160 mmHg and >20 mmHg increase from baseline	809/770 analyses
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

Table 12-6 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
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

12.5 Adverse Events of Special Interest

Table 12-4 MedDRA Preferred Terms for Event of Special Interest

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

Note: The preferred terms listed in the table is based on the MedDRA version 24.1 applicable at the time of finalization of the SAP. If the MedDRA version is upgraded at the time of the final analysis, the corresponding preferred terms based on the upgraded version will be used in the analysis of adverse events of special interest.

12.6 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. Details of the derivation of the GLI equation are provided in the article by Quanjer et al. (2012).

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 April 9, 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 April 9, 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 April 9, 2018].

Data handling rule for spirometry is as follows:

- Input age with at least 2 decimal places
- Use height at screening of the parent study regardless if height is collected at other study visits for subjects whose age at informed consent of the parent study 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 CRF black or AA 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.

Signature Page for VV-TMF-561467 v1.0

Signature Page for VV-TMF-561467 v1.0