VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX20-121-102 Version 3.0
(Final Analysis)

A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-121 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for *F508del* and a Minimal Function Mutation (F/MF)

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Version: 1.0
Version Date of SAP: 18 September 2023

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2 MODIFICATIONS

2.1 Modifications to the Approved Clinical Study Protocol

Not Applicable.

2.2 Modifications to the Approved Statistical Analysis Plan

This is the first version of the Statistical Analysis Plan.

2.3 Modifications to the Approved DMC Charter

Not Applicable.

3 INTRODUCTION

This statistical analysis plan (SAP) is the planned statistical analysis for Study VX20-121-102 (Study 102) and is based on the most recent approved clinical study protocol (CSP), the most recent approved electronic case report form (eCRF), and the most recent eCRF completion guidelines.

Study 102 is a Phase 3, randomized, double-blind, elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)-controlled, parallel group, multicenter study evaluating the efficacy and safety of vanzacaftor (VX-121)/tezacaftor/deutivacaftor (VNZ/TEZ/D-IVA) in cystic fibrosis (CF) subjects who are heterozygous for *F508del* and a minimal function mutation (F/MF). This SAP (Methods) documents the planned final analyses and data presentation for Study 102. For some of these analyses, the Study 102 data are pooled with data from Study VX20-121-103 (Study 103) which is running in parallel with a similar study design and aims to evaluate similar outcomes using a different patient population.

The Vertex Pharmaceuticals Incorporated (Vertex) Biometrics Department will perform the statistical analysis of the efficacy and safety data. SAS® Version 9.4 Software (SAS Institute, Cary, North Carolina, USA) or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets).

The SAP (Methods) will be finalized and approved prior to clinical database lock and treatment unblinding. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP prior to the clinical database lock.

The analysis addressing the pharmacokinetic (PK) objective of the study will be described in the Clinical Pharmacology Analysis Plan which will be developed separately by the Clinical Pharmacology department at Vertex.

4 STUDY OBJECTIVES

4.1 Primary Objective

To evaluate the efficacy of VNZ/TEZ/D-IVA in CF subjects who are heterozygous for *F508del* and a minimal function mutation (F/MF subjects)

4.2 Secondary Objectives

- To evaluate the safety of VNZ/TEZ/D-IVA
- To evaluate the PK of VNZ/TEZ/D-IVA

5 STUDY ENDPOINTS

5.1 Primary Endpoint

Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) through Week 24

5.2 Key Secondary Endpoints

- Absolute change from baseline in sweat chloride (SwCl) through Week 24

- Proportion of subjects with SwCl <60 mmol/L through Week 24 (pooled with data from Study 103)
- Proportion of subjects with SwCl <30 mmol/L through Week 24 (pooled with data from Study 103)

5.3 Other Secondary Endpoints

- Number of pulmonary exacerbations (PEx) through Week 52
- Absolute change from baseline in Cystic Fibrosis Questionnaire – Revised (CFQ-R) Respiratory Domain (RD) score through Week 24
- Absolute change from baseline in $ppFEV_1$ through Week 52
- Absolute change from baseline in SwCl through Week 52
- Proportion of subjects with SwCl <60 mmol/L through Week 24
- Proportion of subjects with SwCl <30 mmol/L through Week 24
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, electrocardiograms (ECGs), vital signs, and pulse oximetry

5.4 Other Endpoints

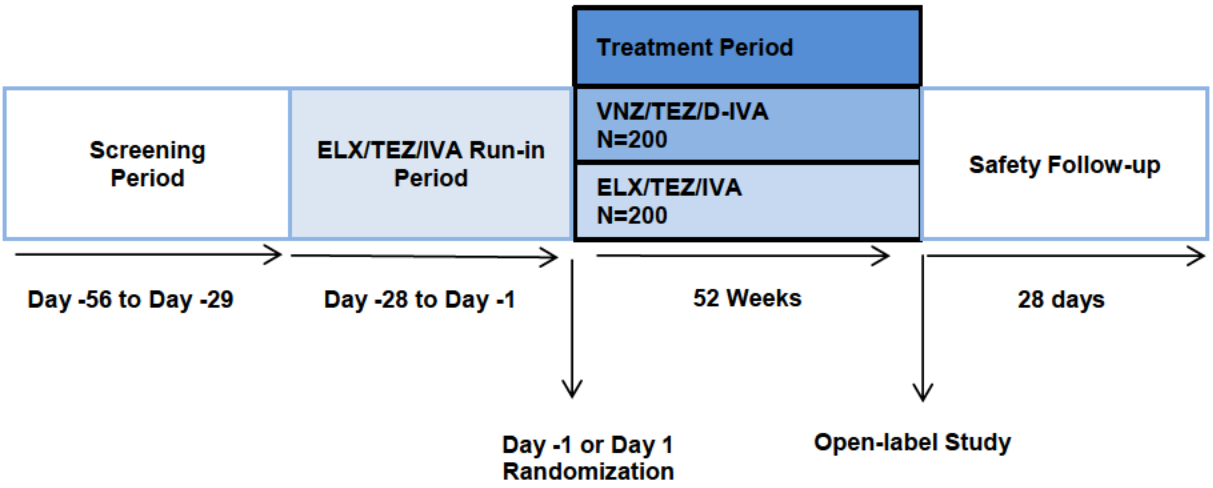
- Proportion of subjects with SwCl <60 mmol/L through Week 52
- Proportion of subjects with SwCl <30 mmol/L through Week 52
- Absolute change from baseline in body mass index (BMI) at Week 52
- Absolute change from baseline in BMI z-score at Week 52
- Absolute change from baseline in weight at Week 52
- Absolute change from baseline in CFQ-R RD score through Week 52
- PK parameters of VNZ, TEZ, and D-IVA

6 STUDY DESIGN

6.1 Overall Design

Study 102 is a Phase 3, randomized, double-blind, ELX/TEZ/IVA-controlled, parallel-group, multicenter study. A schematic of the study design is provided in Figure 6-1.

Figure 6-1 Schematic View of the Study Design



D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor; VNZ: vanzacaftor
Note: The figure is not drawn to scale.

Approximately 400 subjects will be enrolled and randomized.

All subjects entering the Run-in Period will receive ELX 200 mg once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h). Following completion of the Run-in Period, subjects will be randomized (1:1) to the VNZ/TEZ/D-IVA group or the ELX/TEZ/IVA group for the Treatment Period. The dosages to be evaluated are shown in Table 6-1. Randomization will be stratified; details are provided in 6.3.

Table 6-1 Treatment Groups and Dosages

Treatment Group	VNZ	ELX	TEZ	D-IVA	IVA
VNZ/TEZ/D-IVA	20 mg qd	0 mg	100 mg qd	250 mg qd	0 mg
ELX/TEZ/IVA	0 mg	200 mg qd	100 mg qd	0 mg	150 mg q12h

D-IVA: deutivacaftor, ELX: elexacaftor, IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor; VNZ: vanzacaftor

6.2 Sample Size and Power

6.2.1 Power for Primary Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the absolute change from baseline in $ppFEV_1$ through Week 24. The primary null hypothesis to be tested is that the mean absolute change in $ppFEV_1$ from baseline through Week 24 for VNZ/TEZ/D-IVA is inferior by >3 percentage points compared to ELX/TEZ/IVA.

The non-inferiority margin represents a clinically acceptable loss of effectiveness as outlined in regulatory guidances. Furthermore, a statistical approach using the Rothmann method recommends that the non-inferiority margin preserve at least 50% of the treatment effect of the active control (ELX/TEZ/IVA) compared to placebo, where the treatment effect is estimated by the lower bound of the 95% confidence interval (CI)[1,2]. In the overall population eligible for this

study, the lower bound of the 95% CI of the treatment effect for ELX/TEZ/IVA is approximately 12 percentage points for $ppFEV_1$. The selected non-inferiority margin of 3 percentage points is consistent with this statistical method and the non-inferiority margin for $ppFEV_1$ used in clinical studies evaluating symptomatic CF treatments[3,4].

The null hypothesis will be tested at a 1-sided significance level of 0.025.

Assuming a within-group standard deviation (SD) of 8 and a 10% drop-out rate at Week 24 and a treatment difference of 0 between VNZ/TEZ/D-IVA and ELX/TEZ/IVA, a sample size of 200 subjects in each group for a total of 400 subjects will have more than 90% power to test the primary hypothesis for the primary endpoint, based on a 1-sided, 2-sample *t*-test at a significance level of 0.025.

6.2.2 Power for Analysis of Selected Key Secondary Efficacy Endpoint

A key secondary efficacy endpoint is the absolute change from baseline in SwCl through Week 24. Assuming a within-group SD of 14 mmol/L and a 10% drop-out rate at Week 24, a sample size of 200 subjects in each treatment group will have more than 90% power to detect a difference between the treatment groups of -5 mmol/L for the absolute change from baseline in SwCl through Week 24, based on a 2-sided, 2-sample *t*-test at a significance level of 0.05.

6.3 Randomization

Approximately 400 subjects will be randomized (1:1) to the VNZ/TEZ/D-IVA group or the ELX/TEZ/IVA group. Randomization will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), $ppFEV_1$ determined during the Run-in Period (Day -14 clinic assessment; <70 versus ≥70 percentage points), SwCl determined during the Run-in Period (Day -14 assessment; <30 versus ≥30 mmol/L), and prior CFTR modulator use (yes versus no).

6.4 Blinding and Unblinding

This is a double-blind study. Please refer to Section 10.7 of the Study 102 CSP for details.

7 ANALYSIS SETS

7.1 All Subjects Set

The **All Subjects Set** will include all subjects who were randomized or received at least 1 dose of study drug. This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

7.2 Full Analysis Set

The **Full Analysis Set** (FAS) will include all randomized subjects who carry the intended *CFTR* genotype and received at least 1 dose of study drug during the Treatment Period. The FAS will be used to summarize subject demographics and baseline characteristics and for analyses of all efficacy endpoints in which subjects will be analyzed according to their randomized treatment group, unless otherwise specified.

7.3 Pooled Full Analysis Set

The **Pooled Full Analysis Set** (PFAS) will include all randomized subjects from this study (Study 102) and from Study 103 who carry the intended *CFTR* genotype and received at least 1

dose of study drug during the Treatment Period. The PFAS will be used only for pooled analysis of selected endpoints.

7.4 Safety Set

The **Safety Set for the Run-in Period** will include all subjects who received at least 1 dose of ELX/TEZ/IVA during the Run-in Period. This safety set will be used for safety-related outputs during the Run-in Period, unless otherwise specified.

The **Safety Set for the Treatment Period** will include all subjects who received at least 1 dose of study drug during the Treatment Period. This safety set will be used for all safety analyses during the Treatment Period in which subjects will be analyzed according to the treatment they actually received, unless otherwise specified.

8 STATISTICAL ANALYSIS

8.1 General Considerations

The Schedule of Assessments is provided in the CSP for Study 102. 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:

For all safety endpoints:

- Unless otherwise specified, baseline will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the Treatment Period (i.e., the Day 1 Visit).

For all efficacy endpoints:

- Except for SwCl, baseline will be defined as the pre-dose Day 1 value. If the pre-dose Day 1 value is missing, the most recent pre-dose, non-missing value on or after the Day -14 visit, including unscheduled visits, will be used as baseline.
- For SwCl, baseline will be defined as the average of the two most recent pre-dose, non-missing values on or after the Day -14 visit, including unscheduled visits. If only 1 non-missing value is available during this interval, the available value will be considered as baseline.

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

Relative change from baseline will be calculated as (post-baseline value - baseline value)/baseline value.

The **Treatment-emergent (TE) Period for the Run-in Period** will be from the first dose date of study drug in the Run-in Period to (1) the first dose date of study drug in the Treatment Period for subjects who complete the Run-in Period and continue to the Treatment Period, or (2) 28 days after the last dose date of study drug in the Run-in Period or to the completion of study participation date, whichever occurs first, for subjects who do not continue to the Treatment Period (e.g., subjects who do not meet the conditions to enter the Treatment Period).

The **TE Period for the Treatment Period** will be from the first dose date of study drug in the Treatment Period (VNZ/TEZ/D-IVA or ELX/TEZ/IVA) to 28 days after the last dose date of study drug in the Treatment Period or to the completion of study participation date, whichever occurs first.

The **PEx analysis period through Week 52** will be from the first dose date of study drug in the Treatment Period to the last efficacy assessment, which may be collected up to the Week 52 Visit or the earlier of Day 365 and the completion of study participation date if a subject does not have the Week 52 Visit.

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 and maximum and minimum change from baseline values during the TE Period for the Treatment 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 .

Incomplete/missing data: Details on how to handle missing data are described in subsequent sections when applicable.

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

Multiplicity: The multiplicity adjustment procedure for the primary and key secondary endpoints is described in 8.3.2.3. All other *P* values are nominal.

8.2 Background Characteristics

8.2.1 Subject Disposition

A disposition table will be provided for the Run-in Period with the following categories:

- All Subjects Set
- Safety Set for the Run-in Period

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

- Completed Run-in Period treatment
- Prematurely discontinued Run-in Period treatment and the reason for treatment discontinuation
- Prematurely discontinued study in the Run-in Period and the reason for study discontinuation

A separate disposition table will be provided for the Treatment Period with the following categories:

- Randomized
- Safety Set for the Treatment Period
- Full Analysis Set (FAS)
- Randomized but not dosed

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

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

A listing will be provided for subjects who discontinued treatment (including both the Run-in Period and the Treatment Period) or who discontinued study with reasons for discontinuation.

8.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group and overall based on the FAS.

Demographic data will include the following:

- Age at Day 1 (in years)
- Sex (male; female)
- Ethnicity (Hispanic or Latino; Not Hispanic or Latino; Not Collected per Local Regulations)
- Race (White; Black or African American; Northeast Asian; Southeast Asian; Other Asian; Asian (Region Not Reported); American Indian or Alaska Native; Native Hawaiian or Other Pacific Islander; Other; Multiracial; Not Collected per Local Regulations)
- Geographic region (North America [including United States]; Rest of the World [including Europe, Israel, Australia, and New Zealand])

Baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- BMI z-score (for subjects ≤20 years old at Baseline)

Stratification categories will include the following:

- Age at the Screening Visit (<18; ≥18 years)

- $ppFEV_1$ at Day -14 (<70; ≥70 percentage points)
- SwCl at Day -14 (<30; ≥30 mmol/L)
- Prior CFTR modulator Use (Yes; No)

Disease characteristics will include the following:

- $ppFEV_1$ at baseline (<40; ≥ 40 to <70; ≥70 to ≤90; >90 percentage points)
- $ppFEV_1$ at baseline (continuous)
- Sweat chloride at baseline (<30; ≥30 to <60; ≥60 mmol/L)
- Sweat chloride at baseline (continuous)
- CFQ-R respiratory domain score at baseline (adult and child version only) (continuous)
- Prior use of dornase alfa before first dose of study drug in the Treatment Period (Yes; No)
- Prior use of azithromycin before first dose of study drug in the Treatment Period (Yes; No)
- Prior use of inhaled antibiotic before first dose of study drug in the Treatment Period (Yes; No)
- Prior use of any bronchodilator before first dose of study drug in the Treatment Period (Yes; No)
- Prior use of inhaled hypertonic saline before first dose of study drug in the Treatment Period (Yes; No)
- Infection with *Pseudomonas aeruginosa* within 2 years prior to screening (Positive; Negative)

In addition, data listings will also be provided for:

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

8.2.3 Medical History

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

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

8.2.4 Prior and Concomitant Medications

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

Prior medication: any medication that was administered during the 56 days before the first dose of study drug in the Treatment Period excluding the ones that started in the Run-in Period. For subjects who discontinue during the Run-in Period and whose first dose of study drug in the Treatment Period is not available, prior medication will be any medication that was administered during the 56 days before the last dose of study drug in the Run-in Period excluding the ones that started after the first dose in the Run-in Period.

Concomitant medication during the Run-in Period: medication continued or newly received during the TE Period for the Run-in Period

Concomitant medication during the Treatment Period: medication continued or newly received during the TE Period for the Treatment Period

Post-treatment medication: medication continued or newly received after:

- the TE Period for the Run-in Period if the subject did not receive study drug in the Treatment Period
- the TE Period for the Treatment Period for subjects who received study drug in the Treatment Period

A given medication may be classified as any combination of the above categories: for example, prior and concomitant during the Run-in Period, concomitant during the Treatment Period and post-treatment, or concomitant for both periods and post-treatment.

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

Prior medications and concomitant medications will be summarized descriptively for the FAS using frequency tables by: 1) treatment group and overall, Preferred Name (PN); and 2) treatment group and overall, Anatomical Therapeutic Chemical class (ATC) level 1, ATC level 2, and PN.

Prior medications and concomitant medications during the Run-in Period will be summarized together in one summary table. Post-treatment medications will be listed in the all medications listing.

8.2.5 Study Drug Exposure

Study drug exposure will be summarized by treatment group and overall for the Treatment Period only based on the Safety Set for the Treatment Period.

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

Study drug exposure (in weeks) will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized by interval (≤1 week; >1 to ≤2 weeks; >2 to ≤4 weeks; >4 to ≤12 weeks; >12 to ≤24 weeks; >24 to ≤36 weeks; >36 to ≤52 weeks; >52 weeks) using counts and percentages. 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.

8.2.6 Study Drug Compliance

Study drug compliance will be summarized by treatment group and overall for the Treatment Period only based on the FAS.

Study drug compliance will be calculated as: 100 × [1 - (total number of days of study drug interruption during the Treatment Period) / (duration of study drug exposure in days during the Treatment Period)]. 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 descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized in categories (<80%; ≥80%) using frequency tables.

8.2.7 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that may significantly impact the completeness, accuracy, or reliability of key study data or that may significantly affect a subject's rights, safety or well-being. IPDs will be identified by the PD review team according to the protocol deviation plan which will be finalized before the database lock.

IPDs will be summarized descriptively based on the FAS and presented by treatment group and overall. Additionally, IPDs will be provided in an individual subject data listing.

8.3 Efficacy Analysis

All efficacy analyses described in this section will be based on the FAS, unless otherwise specified. The analysis of the below secondary endpoints will be performed based on the PFAS in order to increase the power for the analyses:

- Proportion of subjects with SwCl <60 mmol/L through Week 24 (pooled with data from Study 103)
- Proportion of subjects with SwCl <30 mmol/L through Week 24 (pooled with data from Study 103)

The primary and key secondary endpoints will be formally tested for statistical significance, and the tests will be subject to multiplicity control (see 8.3.2.3 for details). The endpoints involving $ppFEV_1$ and SwCl which are not primary or key secondary will be supportive and analyzed similarly to the corresponding primary and key secondary endpoints; the *P* value presented will be nominal.

8.3.1 Analysis of Primary Efficacy Variable

8.3.1.1 Definition of Primary Efficacy Variable

The primary efficacy variable is the absolute change from baseline in $ppFEV_1$ through Week 24 (estimated by averaging Weeks 16 and 24). Percent predicted FEV_1 is the ratio of observed FEV_1 (L) and predicted FEV_1 (L), expressed as a percentage. See Appendix for more details.

8.3.1.2 Definition of Primary Estimand

The primary estimand is defined as the following and is presented in Appendix :

- Treatment: VNZ/TEZ/D-IVA versus ELX/TEZ/IVA
- Population: Study population represented by inclusion and exclusion criteria
- Variable: Absolute change from baseline (after ELX/TEZ/IVA run-in) in $ppFEV_1$ through Week 24 (estimated by averaging Weeks 16 and 24)
- Handling of intercurrent events (ICE):
    - The treatment policy strategy will be used to handle the use of non-study drug CFTR modulators for >3 days in either the Run-in Period or the Treatment Period prior to Week 24, which means that observed $ppFEV_1$ values will be used, if available, after this prohibited medication use.
    - The treatment policy strategy will be used to handle treatment discontinuation prior to Week 24, which means that observed $ppFEV_1$ values will be used, if available, after treatment discontinuation.
- Population level summary: Difference in variable means between VNZ/TEZ/D-IVA and ELX/TEZ/IVA groups

8.3.1.3 Primary Analysis

The primary null hypothesis to be tested is that the mean for the primary efficacy variable for VNZ/TEZ/D-IVA is inferior by >3 percentage points compared to ELX/TEZ/IVA. The primary analysis of the primary estimand will be performed using a mixed-effects model for repeated measures (MMRM) with change from baseline at Day 15, Week 4, Week 8, Week 16, and Week 24 as the dependent variable. The model will include fixed categorical effects for treatment, visit, age at screening (<18 versus ≥18 years of age), and treatment-by-visit interaction, with baseline $ppFEV_1$ and baseline SwCl as continuous covariates. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the *F*-test for fixed effects will be estimated using the Kenward-Roger approximation[5]. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, an alternative covariance structure like compound symmetry will be used. Conditional on the observed data and covariates, missing data will be assumed to be missing at random (MAR).

The primary result obtained from the model will be the estimated treatment difference through Week 24 (estimated by averaging Weeks 16 and 24). The adjusted mean with a 2-sided 95% CI and the 1-sided *P* value for non-inferiority will be provided. The primary null hypothesis will be rejected, and non-inferiority demonstrated, if the lower bound of the CI is ≥-3.0.

The primary null hypothesis of non-inferiority described above will be tested based on the FAS.

If non-inferiority for the primary endpoint is demonstrated, and if the lower bound of the same 95% CI is greater than 0, then superiority for the primary endpoint is also demonstrated, and the 2-sided *P* value for superiority will be presented.

The estimated within-group change from baseline and treatment difference at each post-baseline visit, obtained from the model, will be provided. The estimated within-group change and its standard error (SE) at each post-baseline visit will also be plotted by treatment group.

8.3.1.4 Supplementary Analysis

8.3.1.4.1 Alternative Estimand using Hypothetical Strategy

An alternative estimand will be defined similarly to the primary estimand with the exception that ICE will be addressed using the hypothetical strategy. In the hypothetical strategy, observed values after ICE will be set to missing to provide a conservative and robust test of non-inferiority for the primary endpoint. Supplementary analysis of this alternative estimand will be performed similarly to the primary analysis as specified in 8.3.1.3. Additional details are presented in Appendix .

8.3.1.5 Subgroup Analysis

Subgroup analyses of the primary efficacy endpoint will be performed for each of the following subgroups:

- Age at screening (<18; ≥18 years)
- $ppFEV_1$ at baseline (<70; ≥70 percentage points)
- SwCl at baseline (<30; ≥30 mmol/L)
- Sex (male; female)
- Geographic region (North America [including United States]; Rest of the World [including Europe, Israel, Australia, and New Zealand])

The MMRM used for the primary analysis of the primary estimand (8.3.1.3) will be used for the subgroup analyses, where the same model will be applied to each category of the subgroup. Note that for the subgroup analysis based on age, the term age at screening (<18 versus ≥18 years of age) will be removed from the MMRM. The adjusted means with 2-sided 95% CIs will be provided. Furthermore, the estimated treatment difference through Week 24 (estimated by averaging Weeks 16 and 24) in different categories within a subgroup will also be presented in a forest plot. Note: The results from the subgroup analyses should be interpreted with caution in the cases where sample sizes are small.

8.3.2 Analysis of Key Secondary Efficacy Variables

The tests for absolute change from baseline in SwCl through Week 24 (continuous variable) based on the FAS and the proportion of subjects with SwCl <60 mmol/L and SwCl <30 mmol/L through Week 24 based on the PFAS will be subject to multiplicity control. Note that the within-study analyses of the proportion of subjects with SwCl <60 mmol/L through Week 24 and the proportion of subjects with SwCl <30 mmol/L through Week 24 based on the FAS are Other Secondary Endpoints and are not subject to multiplicity control; analyses of these endpoints are described in 8.3.3.

8.3.2.1 Definition of Variables

Sweat chloride (SwCl): The SwCl value at 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

>160 mmol/L will be considered missing. Any sweat chloride values reported as <10 mmol/L will be imputed as 10 mmol/L.

8.3.2.2 Analysis Method

Absolute change from baseline in SwCl through Week 24:

The estimand for the absolute change from baseline (after ELX/TEZ/IVA run-in) in SwCl through Week 24 is defined as the following:

- Treatment: VNZ/TEZ/D-IVA versus ELX/TEZ/IVA
- Population: Study population represented by inclusion and exclusion criteria
- Variable: Absolute change from baseline in SwCl through Week 24 (estimated by averaging Weeks 16 and 24)
- Handling of ICE: Same as the primary estimand (8.3.1.2)
- Population level summary: Difference in variable means between VNZ/TEZ/D-IVA and ELX/TEZ/IVA groups

The analysis of absolute change from baseline in SwCl through Week 24 will be based on an MMRM similar to the primary analysis of the primary estimand (8.3.1.3), with absolute change from baseline in SwCl at Day 15, Week 4, Week 16, and Week 24 as the dependent variable. The estimated treatment difference through Week 24 (estimated by averaging Weeks 16 and 24) will be presented along with the 2-sided 95% CI and *P* value. The estimated within-group change from baseline and treatment difference at each post-baseline visit, obtained from the model, will be provided. The estimated within-group change and its SE at each post-baseline visit will also be plotted by treatment group.

Proportion of subjects with SwCl <60 mmol/L through Week 24 (pooled with data from Study 103):

The estimand for the proportion of subjects with SwCl <60 mmol/L through Week 24 is defined as the following:

- Treatment: VNZ/TEZ/D-IVA versus ELX/TEZ/IVA
- Population: Pooled study population represented by inclusion and exclusion criteria
- Variable: Response defined as SwCl <60 mmol/L through Week 24 (estimated by averaging Weeks 16 and 24)
- Handling of ICE: Same as the primary estimand (8.3.1.2)
- Population level summary: Odds ratio comparing the response rates in VNZ/TEZ/D-IVA and ELX/TEZ/IVA groups

The response corresponding to SwCl <60 mmol/L at each visit through Week 24 in the PFAS will be analyzed using a generalized estimating equations (GEE) model. The model will include fixed categorical effects for treatment, age at screening (<18 versus ≥18 years of age), genotype group (F/MF, F/F, F/G, F/RF, TCR/non-F), visit, and treatment-by-visit interaction, with baseline ppFEV$_1$ and baseline SwCl as continuous covariates. A logit link function and an unstructured working correlation matrix will be used in the GEE model. If the model estimation

does not converge, genotype group will be considered with three levels (F/MF, F/F and Other) or removed from the model, and if non-convergence persists, an alternative covariance structure like compound symmetry will be used. The estimated odds ratio through Week 24 (estimated by averaging Weeks 16 and 24) along with the 2-sided 95% CI and *P* value will be presented. The estimates for each visit through Week 24 will also be presented. The number and proportion of subjects with SwCl <60 mmol/L at each post-baseline visit through Week 24 will be descriptively summarized by treatment group.

Proportion of subjects with SwCl <30 mmol/L through Week 24 (pooled with data from Study 103):

The estimand and analysis will be similar to that for the pooled analysis of proportion of subjects with SwCl <60 mmol/L through Week 24.

8.3.2.3 Multiplicity Adjustment

A hierarchical testing procedure will be used to control the overall type I error at an alpha of 0.05. The key secondary endpoints will be formally tested at an alpha level of 0.05 only if the primary analysis of absolute change from baseline in ppFEV$_1$ through Week 24 is statistically significant, i.e., if the null hypothesis of inferiority has been rejected. For a test at any step to be considered statistically significant within the testing hierarchy, it must be statistically significant, and all previous tests (if any) within the hierarchy must be statistically significant at the 0.05 level (one-sided 0.025 level for the primary endpoint). The testing order of the key secondary endpoints is as follows:

- Absolute change from baseline in SwCl through Week 24
- Proportion of subjects with SwCl <60 mmol/L through Week 24 (pooled with data from Study 103)
- Proportion of subjects with SwCl <30 mmol/L through Week 24 (pooled with data from Study 103)

8.3.3 Analysis of Other Secondary Variables

8.3.3.1 Definition of Variables

Pulmonary exacerbation (PEx): A PEx is defined as a new 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 through Week 52 is defined as the total number of PEx during the PEx analysis period (defined in 8.1).

Cystic Fibrosis Questionnaire – Revised (CFQ-R): The CFQ-R[6, 7, 8] 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 (subjects 13 years and younger on the date of informed consent)
- CFQ-R for Adolescents and Adults (subjects 14 years and older on the date of informed consent)
- CFQ-R for Parents/Caregivers (subjects 13 years and younger on the date of informed consent)

In all three versions, specific questions belonging to a domain are 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 Adolescents and Adults will be pooled for analysis purposes.

8.3.3.2 Analysis Method

Number of PEx through Week 52: The number of PEx through Week 52 will be analyzed, and the estimated PEx rate (per year, with 48 weeks as 1 year) will be presented. The difference in PEx rate and the associated 95% CI will also be provided.

Absolute change from baseline in CFQ-R Respiratory Domain (RD) score through Week 24: The analysis of absolute change from baseline in CFQ-R RD score through Week 24 will be based on an MMRM similar to the primary analysis of the primary estimand (8.3.1.3), with absolute change from baseline in CFQ-R RD score at Week 8, Week 16, and Week 24 as the dependent variable. The estimated treatment difference through Week 24 (estimated by averaging Weeks 16 and 24) will be presented along with the 2-sided 95% CI. The estimated within group change from baseline and treatment difference at each post-baseline visit, obtained from the model, will be provided.

Absolute change from baseline in ppFEV$_1$ through Week 52: Analysis of this endpoint will be based on an MMRM similar to the primary analysis of the primary estimand (8.3.1.3), with the addition of data from Week 36 and Week 52. The estimated change through Week 52 will be based on averaging estimates from Weeks 16, 24, 36 and 52. The post-baseline raw values and the absolute change from baseline at each post-baseline visit through Week 52 will be summarized descriptively (n, mean, SD, median, min, max).

Absolute change from baseline in SwCl through Week 52: Analysis of this endpoint will be based on an MMRM similar to that for absolute change from baseline in SwCl through Week 24 (8.3.2.2), with the addition of data from Week 36 and Week 52. The estimated change through Week 52 will be based on averaging estimates from Weeks 16, 24, 36 and 52. The post-baseline raw values and the absolute change from baseline at each post-baseline visit through Week 52 will be summarized descriptively (n, mean, SD, median, min, max).

Proportion of subjects with SwCl <60 mmol/L through Week 24 (within-study): Analysis of this endpoint will be based on a GEE model similar to that for the proportion of subjects with SwCl <60 through Week 24 using the PFAS (8.3.2.2), but instead will be based on the FAS. Genotype group will not be included in the model since all subjects in Study 102 will be F/MF.

Proportion of subjects with SwCl <30 mmol/L through Week 24 (within-study): Analysis of this endpoint will be based on a GEE model similar to that for the proportion of subjects with SwCl <30 through Week 24 using the PFAS (8.3.2.2), but instead will be based on the FAS. Genotype group will not be included in the model since all subjects in Study 102 will be F/MF.

8.3.4 Analysis of Other Endpoints

8.3.4.1 Definition of Variables

Body Mass Index (BMI): The BMI at each visit is calculated using the weight and height at each visit as follows:

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

BMI z-score: The BMI-for-age z-score, adjusted for age and sex, will be referred to as BMI z-score. The BMI z-score will be calculated using the Centers for Disease Control and Prevention (CDC) growth charts[9], with age (in months) used for the calculation defined in Appendix .

8.3.4.2 Analysis Method

Proportion of subjects with SwCl <60 mmol/L through Week 52 (within-study): Analysis of this endpoint will be based on a GEE model similar to that for the proportion of subjects with SwCl <60 through Week 24 using the FAS (8.3.3.2), with the addition of data from Week 36 and Week 52.

Proportion of subjects with SwCl <30 mmol/L through Week 52 (within-study): Analysis of this endpoint will be based on a GEE model similar to that for the proportion of subjects with SwCl <30 through Week 24 using the FAS (8.3.3.2), with the addition of data from Week 36 and Week 52.

Absolute change from baseline in BMI at Week 52: Analysis of this variable will be based on an MMRM similar to the primary analysis of the primary estimand (8.3.1.3). Data obtained from Day 15, Week 4, Week 8, Week 16, Week 24, Week 36, and Week 52 will be included in the

model. The estimated treatment difference at Week 52 will be presented along with the 2-sided 95% CI. The post-baseline raw values and the absolute change from baseline at each post-baseline visit through Week 52 will be summarized descriptively (n, mean, SD, median, min, max), in addition.

Absolute change from baseline in BMI z-score at Week 52 (for subjects ≤20 years of age at Baseline): Analysis of this variable will be based on an MMRM similar to the primary analysis of the primary estimand (8.3.1.3), excluding the term age at screening (<18 versus ≥18 years of age), for subjects ≤20 years of age at Baseline. Data obtained from Day 15, Week 4, Week 8, Week 16, Week 24, Week 36, and Week 52 will be included in the model. The estimated treatment difference at Week 52 will be presented along with the 2-sided 95% CI. The post-baseline raw values and the absolute change from baseline at each post-baseline visit through Week 52 will be summarized descriptively (n, mean, SD, median, min, max), in addition.

Absolute change from baseline in weight at Week 52: Analysis of this variable will be based on an MMRM similar to the primary analysis of the primary estimand (8.3.1.3). Data obtained from Day 15, Week 4, Week 8, Week 16, Week 24, Week 36, and Week 52 will be included in the model. The estimated treatment difference at Week 52 will be presented along with the 2-sided 95% CI. The post-baseline raw values and the absolute change from baseline at each post-baseline visit through Week 52 will be summarized descriptively (n, mean, SD, median, min, max), in addition.

Absolute change from baseline in CFQ-R RD score through Week 52: Analysis of this domain will be based on an MMRM similar to that for absolute change from baseline in CFQ-R RD score through Week 24 (8.3.3.2), with the addition of data from Week 52. The estimated change through Week 52 will be based on averaging estimates from Weeks 16, 24, and 52. The estimated treatment difference through Week 52 will be presented along with the 2-sided 95% CI. The post-baseline raw values and the absolute change from baseline at each post-baseline visit through Week 52 will be summarized descriptively (n, mean, SD, median, min, max), in addition.

8.3.5 Analysis of Additional Efficacy Variables

8.3.5.1 Analysis of Additional Spirometry Variables

Summary statistics for raw values and for change from baseline of the following spirometry measurements will be presented by treatment group at each visit:

- FEV_1:
  - Absolute change from baseline in FEV_1 (L)
  - Relative change from baseline in FEV_1 (%)
  - Absolute change from baseline in percent predicted FEV_1 (percentage points)
  - Relative change from baseline in percent predicted FEV_1 (%)
- FVC:
  - Absolute change from baseline in FVC (L)
  - Relative change from baseline in FVC (%)
  - Absolute change from baseline in percent predicted FVC (percentage points)

- Relative change from baseline in percent predicted FVC (%)

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

8.3.5.2 Analysis of Other CFQ-R Variables

Descriptive summary statistics for raw values and for change from baseline of the CFQ-R non-respiratory domain scores will be presented by treatment group at each visit.

8.3.5.3 Analysis of Additional Variables for Pulmonary Exacerbations and Hospitalization

The analysis period for all variables in this section will be the PEx analysis period.

Pulmonary Exacerbations:
In addition to the other secondary endpoint described in 8.3.3.2, PEx will be further analyzed as described below:

- Time-to-first event (in days):
  - Time-to-first PEx
  - Time-to-first PEx requiring hospitalization
  - Time-to-first PEx requiring intravenous (IV) antibiotic therapy
  - Time-to-first PEx requiring hospitalization or IV antibiotic therapy
- Number of events:
  - Number of PEx requiring hospitalizations through Week 52
  - Number of PEx requiring IV antibiotic therapy through Week 52
  - Number of PEx requiring hospitalization or IV antibiotic therapy through Week 52
- Duration of events:
  - Number of days with PEx through Week 52
  - Number of days with PEx requiring hospitalization through Week 52
  - Number of days with PEx requiring IV antibiotic therapy through Week 52
  - Number of days with PEx requiring hospitalization or IV antibiotic therapy through Week 52

Hospitalization:

- Number of events:
  - Number of planned hospitalizations for CF (i.e., antibiotic therapy) through Week 52

  - Number of all unplanned hospitalizations for reasons other than antibiotic therapy for sinopulmonary signs/symptoms through Week 52

- Duration of events:
  - Number of days of planned hospitalizations for CF (i.e., antibiotic therapy) through Week 52
  - Number of days of all unplanned hospitalizations for reasons other than antibiotic therapy for sinopulmonary signs/symptoms through Week 52

Analysis of PEx/Hospitalization Variables:

For the time-to-event variables, the analysis time will be the number of days from the first dose date of study drug in the Treatment Period to the date of the first defined event during the PEx analysis period. A subject who does not experience the event during the PEx analysis period will be censored at the PEx analysis period end date for that event. The analysis of time-to-event will be based on the Kaplan Meier method; the corresponding plot will be presented.

For the number of events variables, subjects with multiple defined events during the PEx analysis period will be counted multiple times. A descriptive summary of the number of events along with the observed event rate will be provided.

The annualized duration of events for each subject will be the total number of days with the defined event times 48 weeks, divided by the total number of weeks in the study up to the end of the PEx analysis period. The annualized duration will be descriptively summarized.

8.4 Safety Analysis

All safety analyses will be based on data from the TE Period for the Treatment Period for all subjects in the Safety Set for the Treatment Period, unless otherwise specified. Subjects will be analyzed according to the treatment they actually received in the Treatment Period, as applicable. Subjects receiving study drug from more than one treatment group will be allocated to the VNZ/TEZ/D-IVA group.

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

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values
- ECGs
- Vital signs
- Pulse oximetry
- Ophthalmological examinations (for subjects <18 years of age on the date of informed consent)

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

8.4.1 Adverse Events

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

Pretreatment AE: any AE that occurred before the first dose date of study drug in the Run-in Period

TEAE during the Run-in Period: any AE that worsened (either in severity or seriousness) or that was newly developed on or after the first dose date of study drug in the Run-in Period through the end of the TE Period for the Run-in Period

TEAE during the Treatment Period: any AE that worsened (either in severity or seriousness) or that was newly developed on or after the first dose date of study drug in the Treatment Period through the end of the TE Period for the Treatment Period

Post-treatment AE: any AE that worsened (either in severity or seriousness) or that was newly developed after:

- the TE Period for the Run-in Period if the subject did not receive treatment in the Treatment Period
- the TE Period for the Treatment Period if the subject received treatment in the Treatment Period

For AEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs started before or after study treatment, the AEs will be classified as TEAEs corresponding to the Treatment Period. Unless otherwise specified, TEAE refers to TEAE during the Treatment Period.

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

An overview of all TEAEs by treatment group and overall will be summarized in the following categories:

- Number of TEAEs (total number of TEAEs only)
- Subjects with any TEAEs
- Subjects with TEAEs by strongest relationship
- Subjects with TEAEs by maximum severity
- Subjects with TEAEs leading to study drug discontinuation (discontinuation of any study drugs)
- Subjects with TEAEs leading to study drug interruption (interruption of any study drugs)
- Subjects with Grade 3+ 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 by treatment group:

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Grade 3+ TEAEs
- 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 with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once, and only the maximum severity level will be presented in the severity summaries and the strongest relationship level in the relationship summaries.

Additional summary tables will be presented by treatment for TEAEs showing number and percentage of subjects:

- All TEAEs by PT

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

The following tables for the Run-in Period will be presented overall based on the Safety Set for the Run-in Period:

- An overview of TEAEs during the Run-in Period
- All TEAEs during the Run-in Period by SOC and PT

8.4.2 Clinical Laboratory

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

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

For select liver function laboratory tests (alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALP], and total bilirubin), a scatterplot of the maximum TE value versus the baseline value corresponding to xULN (upper limit of normal) will be presented. Further, a scatterplot of the maximum TE value of ALT and AST, separately, versus the maximum TE value of total bilirubin corresponding to xULN will also be presented by treatment group. For ALT, AST, and total bilirubin, box-and-whisker plots will be used to display raw values at each visit by treatment group.

Results of positive serum/urine pregnancy tests will be listed in individual subject data listings only. For the positive serum pregnancy listing, subjects with serum HCG which are abnormally high will be selected.

In addition, listings containing individual subject hematology, chemistry, coagulation, and urinalysis values will be provided. The listings will include data from both scheduled and unscheduled visits. A listing of subjects who meet the criteria of [(ALT>3xULN or AST>3xULN) and TBILI>2xULN] at any visit will be provided. This listing will include data from all visits (including unscheduled visits) and present values for ALT, AST, ALP, and total bilirubin.

8.4.3 Electrocardiogram

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

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE Period for the Treatment Period will be summarized by treatment group. The threshold analysis criteria are provided in Appendix .

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

8.4.4 Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized at each visit by treatment group. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mmHg), body temperature (ºC), pulse rate (beats/minute), and respiratory rate (breaths/minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE Period for the Treatment Period will be summarized by treatment group. The threshold analysis criteria are provided in Appendix .

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

8.4.5 Pulse Oximetry

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

The number and percentage of subjects with shift changes from baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the TE

Period for the Treatment Period will be summarized by treatment group. The reference range for normal oxygen saturation is specified as >95%, and <=95% for low oxygen saturation.

8.4.6 Ophthalmologic Examinations

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

8.4.7 Physical Examination

Abnormal PE findings will be presented in individual subject data listings only.

8.4.8 Supportive Safety Analysis

8.4.8.1 Adverse Events of Special Interest

For this study, elevated transaminases, creatine kinase elevations, rash, cataracts, hypoglycemia, and neuropsychiatric events as determined by MedDRA PTs in Appendix are considered adverse events of special interest (AESI).

For AESI during the TE Period for the Treatment Period, 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 related events
- Subjects with serious events
- Subjects with related serious events
- Subjects with events leading to death
- Duration of events
- Time-to-onset of first event

8.5 Additional Analysis

This section describes analysis of TSQM domains. Analyses of other exploratory assessments mentioned in the protocol may be described in a separate document. The description of analyses of additional variables of SwCl is also included.

8.5.1 Analysis of TSQM Domains

TSQM is a widely used generic measure of satisfaction with medication and has been demonstrated to be a valid and reliable measure of satisfaction in patients with CF[10]. It consists of 14 items to form 4 domains: effectiveness (items 1, 2, 3), side effects (items 4, 5, 6, 7, 8), convenience (items 9, 10, 11), and global satisfaction (items 12, 13, 14). The score of each domain is a scaled score that ranges from 0 (least satisfied) to 100 (most satisfied). Scaled score for each domain can be calculated using the scale scoring algorithm[11].

Absolute change from baseline in TSQM domains at Week 52 (only for subjects aged ≥12 years to <18 years at the date of informed consent) will be analyzed descriptively.

8.5.2 Analysis of Additional Variables for SwCl

Proportion of subjects with SwCl <60 mmol/L through Week 52 (pooled with data from Study 103): Analysis of this endpoint will be based on a GEE model similar to that for the proportion of subjects with SwCl <60 through Week 24 using the PFAS (8.3.2.2), with the addition of data from Week 36 and Week 52.

Proportion of subjects with SwCl <30 mmol/L through Week 52 (pooled with data from Study 103): Analysis of this endpoint will be based on a GEE model similar to that for the proportion of subjects with SwCl <30 through Week 24 using the PFAS (8.3.2.2), with the addition of data from Week 36 and Week 52.

9 SUMMARY OF INTERIM AND DMC ANALYSIS

9.1 Interim Analysis

No interim analysis is planned for this study.

9.2 DMC Analysis

The DMC will conduct planned safety reviews of study data as outlined in the DMC Charter. For the open session of each DMC meeting, selected tables will be presented for the overall treatment group based on blinded data. For the closed session, the analysis presentation will be by treatment group based on unblinded data (generated by the independent biostatistician).

10 REFERENCES

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11 LIST OF APPENDICES

Appendix A: Analysis Visit Windows for Safety and Efficacy Assessments

Table 11-1 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window[2,3,4] (in study days)
Safety Assessments			
• Pulse oximetry • Serum chemistry • Hematology (except HbA1c) • Vital signs (excluding BMI, height, weight)	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 12 Week 16 Week 24 Week 36 Week 52 Safety Follow-up	1 15 29 57 85 113 169 253 365 Not applicable	≤1 Pre-dose [1, 22] (22, 43] (43, 71] (71, 99] (99, 141] (141, 211] (211, 309] (309, 379] Use nominal visit
HbA1c (%)	Day 1 (Baseline) Week 12 Week 24 Week 52	1 85 169 365	≤1 Pre-dose [1, 127] (127, 267] (267, 379]
Standard 12-lead ECG	Day 1 (Baseline) Day 15 Week 4 Week 8 Week 16 Week 24 Week 36 Week 52 Safety Follow-up	1 15 29 57 113 169 253 365 Not applicable	≤1 Pre-dose [1, 22] (22, 43] (43, 85] (85, 141] (141, 211] (211, 309] (309, 379] Use nominal visit
Coagulation	Day 1 (Baseline) Week 12 Week 24 Week 36 Week 52 Safety Follow-up	1 85 169 253 365 Not applicable	≤1 Pre-dose [1, 127] (127, 211] (211, 309] (309, 379] Use nominal visit
Efficacy Assessments[5]			
• Spirometry (in-clinic) • Height, weight, BMI, and z-scores	Baseline Day 15 Week 4 Week 8 Week 16 Week 24 Week 36 Week 52 Safety Follow-up	- 15 29 57 113 169 253 365 Not applicable	≤1 Pre-dose [1, 22] (22, 43] (43, 85] (85, 141] (141, 211] (211, 309] (309, 379] >379

Table 11-1 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window[2,3,4] (in study days)
Sweat Chloride	Baseline	-	≤1 Pre-dose
	Day 15	15	[1, 22]
	Week 4	29	(22, 71]
	Week 16	113	(71, 141]
	Week 24	169	(141, 211]
	Week 36	253	(211, 309]
	Week 52	365	(309, 379]
CFQ-R	Baseline	-	≤1 Pre-dose
	Week 8	57	[1, 85]
	Week 16	113	(85, 141]
	Week 24	169	(141, 267]
	Week 52	365	(267, 379]
TSQM	Baseline	-	≤1 Pre-dose
	Week 52	365	[1, 379]

Notes:

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

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

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

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

a. Scheduled measurements will be treated as pre-dose observations.
b. Unscheduled measurements will be treated as post-dose observations.

[4] For safety assessments, the Safety Follow-up analysis visit will be based on the nominal Safety Follow-up visit. If a subject does not have a nominal Safety Follow-up visit but has an early termination of treatment (ETT) visit with study day >379, then the ETT visit will be mapped to the Safety Follow-up analysis visit.

[5] For efficacy assessments, if a subject has a nominal Safety Follow-up visit with study day >379, then the nominal Safety Follow-up visit will be mapped to the Safety Follow-up analysis visit; else if a subject does not have a nominal Safety Follow-up visit with study day >379 but has an ETT visit with study day >379, then the ETT visit will be mapped to the Safety Follow-up analysis visit; else if there are multiple assessments with study day >379, then the earliest record will be selected as the Safety Follow-up analysis visit.

Derived Variables:

1. Age (in years) at first dose date and at nominal visits (for demographics, listings, 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 15.22 days to convert to days.

   Obtain the informed consent date.

Table 11-1 Analysis Visit Windows for Safety and Efficacy Assessments

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

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 calculation of BMI and z-scores, as applicable):

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

   Obtain the informed consent date.

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

3. Missing first dose date or last dose date:

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

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

4. Sweat Chloride:

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

5. Electrocardiogram:

   Baseline is defined as the most recent pre-treatment measurement before the first dose of study drug in the Treatment Period. If multiple ECG measurements are obtained on the same calendar day during the TE Period for the Treatment Period,

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

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

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

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

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

Table 11-2 Prior, Concomitant, and Post Categorization of a Medication

	Medication Stop Date			
Medication Start Date	< First Dose Date of Run-in TE Period	≥ First Dose Date of Run-in TE Period and < End Date of Run-in TE Period	≥ First Dose Date of Treatment TE Period and ≤ End Date of Treatment TE Period	> End Date of Treatment TE Period
< First Dose Date of Run-in TE Period	P	PC1	PC1C2	PC1C2A
≥ First Dose Date of Run-in TE Period and < End Date of Run-in TE Period	-	C1	C1C2	C1C2A
≥ First Dose Date of Treatment TE Period and ≤ End Date of Treatment TE Period	-	-	C2	C2A
> End Date of Treatment TE Period	-	-	-	A

P: Prior; C1: Concomitant during the Run-in Period; C2: Concomitant during the Treatment Period; A: Post

The same imputation rules will be followed to address missing and/or partial dates for non-pharmacological treatments/procedures.

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

Percent predicted values will be calculated for the 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. Global Lung Function Initiative. [online] Available at: https://www.ers-education.org/lr/show-details/?idP=138978 [Accessed Sep 2023].

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. Global Lung Function Initiative. [online] Available at: https://www.ers-education.org/lr/show-details/?idP=138979 [Accessed Sep 2023].

Sanja Stanojevic. GLI-2012 - SAS Macro. Global Lung Function Initiative. [online] Available at: https://www.ers-education.org/lr/show-details/?idP=138988 [Accessed Sep 2023].

The data handling rule for spirometry is as follows:

- Input age with at least 2 decimal places
- Use height at screening, regardless of 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.
- For race, race is Black if, on the CRF, Black or African American is the only race selected. Race is Northeast Asian if Northeast Asian is the only race selected. Race is Southeast Asian if Southeast Asian is the only race selected. Race is White if White is the only race selected. Race is Other for all other races, including multiple selections.

Appendix D: Estimand Framework for the Primary Efficacy Endpoint

Estimand	**Primary Estimand**	**Alternative Estimand**
Treatment	VNZ/TEZ/D-IVA versus ELX/TEZ/IVA	
Population	Study population represented by inclusion and exclusion criteria	
Variable	Absolute change from baseline in $ppFEV_1$ through Week 24	
Population-level summary	Difference in variable means between VNZ/TEZ/D-IVA and ELX/TEZ/IVA groups	
Handling of ICE		
Treatment discontinuation	Treatment Policy (i.e., observed $ppFEV_1$ values after the ICE will be used, if available)	Hypothetical strategy (i.e., observed $ppFEV_1$ values after the ICE will be set to missing)
Use of prohibited medication[†]		
Analysis	**Primary Analysis**	**Supplementary Analysis**
Analysis model	MMRM	
Intermittent missing	MMRM	
Treatment discontinuation	MMRM	
Use of prohibited medication	MMRM	
Other reasons	MMRM	

D-IVA: deutivacaftor; ELX: elexacaftor; ICE: intercurrent event; IVA: ivacaftor; MMRM: mixed model for repeated measures; TEZ: tezacaftor; VNZ: vanzacaftor

[†] Prohibited medication includes use of non-study drug CFTR modulators for >3 days in either the Run-in Period or the Treatment Period prior to Week 24

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

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

  Compare the imputed AE start date with the TE Period to determine whether the AE is pretreatment AE, TEAE during the Run-in Period, TEAE during the Treatment Period, 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 in the Treatment Period or AE end date is missing, then
        - if AE start year is equal to the year of first dose date in the Treatment Period, then impute the AE start month and day as the month and day of first dose date in the Treatment Period;
        - else, if AE start year is equal to the year of first dose date in the Run-in Period, then impute the AE start month and day as the month and day of first dose date in the Run-in Period;
        - else, impute the AE start month as January and day as 1.
    - Else, if the full (or partial) AE end date is NOT before the first dose date in the Run-in Period, then

        - if AE start year is equal to the year of first dose date in the Run-in Period, then impute the AE start month and day as the month and day of the first dose date in the Run-in Period;
        - else, impute the AE start month as January and day as 1.
    - Else, impute the AE start month as January and day as 1.

  Compare the imputed AE start date with the TE Period to determine whether the AE is pretreatment AE, TEAE during the Run-in Period, TEAE during the Treatment Period, or post-treatment AE.

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

  If the year of AE start date is missing or AE start date is completely missing:

    - If the full (or partial) AE end date is NOT before the first dose date in the Treatment Period or AE end date is missing, then impute the AE start date as the date of first dose date in the Treatment Period.
    - Else, if the full (or partial) AE end date is NOT before the first dose date in the Run-in Period, then impute the AE start date as first dose date in the Run-in Period.
    - Else, impute AE start date as the informed consent date.

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

Imputation rules for partial AE end dates are defined below:

For a partial AE end date, impute 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 F: Criteria for Threshold Analysis

Table 11-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

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 >1.5x – ≤ 2.5xULN >2.5x – ≤ 5x ULN >5x – ≤ 20x ULN >20x ULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>ULN - ≤ 1.5xULN >1.5x – ≤ 2xULN >2x – ≤ 3xULN >3x – ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
Direct Bilirubin	>ULN - ≤ 1.5xULN >1.5x – ≤ 2xULN >2x – ≤ 3xULN >3x – ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
Indirect Bilirubin	>ULN - ≤ 1.5xULN >1.5x – ≤ 2xULN >2x – ≤ 3xULN >3x – ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	FDA DILI Guidance Jul 2009.

Table 11-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
GGT	>ULN - ≤ 2.5xULN >2.5x – ≤ 5xULN >5x – ≤ 20xULN >20xULN	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	>ULN - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Creatinine	>ULN - ≤ 1.5xULN >1.5x - ≤ 3xULN >3x - ≤ 6xULN >6xULN	CTCAE grades 1-4
Lipase	>ULN - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
Creatine Kinase	>ULN - ≤ 2.5xULN >2.5x - ≤ 5xULN >5x - ≤ 10xULN >10xULN	CTCAE grades 1-4
Hematology		
Hemoglobin	Hgb decreased (anemia) <LLN - ≥ 100 g/L <100 – ≥ 80 g/L < 80 g/L	CTCAE grade 1-3
	Hgb increased >ULN - ≤ 20 g/L above ULN >20 g/L above ULN - ≤ 40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3
Platelets	Platelet decreased <LLN - ≥ 75.0 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

Table 11-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Coagulation		
Activated partial thromboplastin time (PTT)	>ULN - ≤ 1.5xULN >1.5x – ≤ 2.5xULN >2.5xULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤ 1.5xULN >1.5x – ≤ 2.5xULN >2.5xULN	CTCAE grade 1-3

Table 11-4 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
HR	Bradycardia <50 beats per minute (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
	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 msec ≥300 msec ≥200 msec and increase from baseline ≥40 msec ≥200 msec and increase from baseline ≥100 msec	
QRS	>110 msec >160 msec Increase from baseline ≥20 msec Increase from baseline ≥40 msec	
QTc	>450 msec and <500 msec (Male); >470 msec and <500 msec (Female) ≥500 msec Increase from baseline >10 msec Increase from baseline >20 msec Increase from baseline >40 msec Increase from baseline >60 msec	To be applied to any kind of QT correction formula.

Table 11-4 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments

Note: Based on CPMP 1997 guideline.

Table 11-5 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
SBP decreased	<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	

Table 11-5 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
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 11-6 Threshold Analysis Criteria for Laboratory Tests

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

Appendix G: Adverse Events of Special Interest

Table 11-7 MedDRA Preferred Terms for Event of Special Interest

Adverse event of special interest	MedDRA preferred terms [1]
Transaminase Elevations	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	AGEP-DRESS overlap, 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, Lichen planus pemphigoides, Mucocutaneous rash, Mucocutaneous toxicity, Nodular rash, Oculomucocutaneous syndrome, Penile dermatitis, Perioral dermatitis, Periorbital 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, Severe cutaneous adverse reaction, Skin exfoliation, Skin necrosis, Skin toxicity, Stevens-Johnson syndrome, Systemic contact dermatitis, Toxic epidermal necrolysis, Toxic skin eruption, Type IV hypersensitivity reaction, Urticaria, Urticaria papular, Urticaria vesiculosa, Urticarial dermatitis, Urticarial vasculitis, Vasculitic rash
Cataracts	Atopic cataract, Cataract, Cataract congenital, Cataract cortical, Cataract diabetic, Cataract nuclear, Cataract subcapsular, Lens discolouration, Lenticular opacities, MYH9-related disease, Radiation cataract, Toxic cataract
Hypoglycemia	Blood glucose decreased, Hypoglycaemia, Glycopenia, Hyperinsulinaemic hypoglycaemia, Hypoglycaemia unawareness, Hypoglycaemic coma, Hypoglycaemic encephalopathy, Hypoglycaemic seizure, Hypoglycaemic unconsciousness, Shock hypoglycaemic
Creatine Kinase Elevations	Blood creatine phosphokinase increased, Blood creatine phosphokinase MM increased, Blood creatine phosphokinase MB increased, Blood creatine phosphokinase BB increased, Muscle enzyme increased, Rhabdomyolysis, Myoglobinuria, Myoglobin urine present
Neuropsychiatric Events	Abnormal behaviour, Adjustment disorder with anxiety, Adjustment disorder with depressed mood, Adjustment disorder with mixed anxiety and depressed mood, Aggression, Agitated depression, Anger, Anhedonia, Anticipatory anxiety, Antisocial behaviour, Anxiety, Anxiety disorder, Assisted suicide, Attention deficit hyperactivity

	disorder, Behaviour disorder, Behavioural insomnia of childhood, Belligerence, Brain fog, Childhood depression, Completed suicide, Decreased interest, Depressed mood, Depression, Depression suicidal, Depressive symptom, Discouragement, Disturbance in attention, Dysania, Dysphoria, Feeling abnormal, Feeling guilty, Feeling of despair, Feelings of worthlessness, Generalised anxiety disorder, Helplessness, Hostility, Illness anxiety disorder, Initial insomnia, Insomnia, Intentional overdose, Intentional self-injury, Irritability, Major depression, Memory impairment, Mental disorder, Mental fatigue, Middle insomnia, Mixed anxiety and depressive disorder, Paradoxical insomnia, Persistent depressive disorder, Physical abuse, Physical assault, Poisoning deliberate, Psychophysiologic insomnia, Self-injurious ideation, Suicidal behaviour, Suicidal ideation, Suicide attempt, Suicide threat, Suspected suicide, Suspected suicide attempt, Terminal insomnia
[1] The preferred terms (PTs) listed in the table are 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 PTs based on the upgraded version will be used in the analysis of adverse events of special interest.	