VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX18-445-113 Version 1.0

A Phase 3, Open-label Study Evaluating the Long-term Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis

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3 INTRODUCTION

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

This SAP (Methods) documents the planned statistical analyses of safety and other endpoints.

The SAP (Methods) will be finalized and approved prior to the clinical database lock for the final analysis. Analyses will be performed separately for Part A and B, unless otherwise specified. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP prior to the clinical database lock for the final analysis. Any changes made to the SAP Methods after the clinical database lock has occurred will be documented in the clinical study report for this study.

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).

4 STUDY OBJECTIVES

4.1 Primary Objective

To evaluate the long-term safety and tolerability of VX-445 (ELX)/ tezacaftor (TEZ)/ ivacaftor (IVA)

5 STUDY ENDPOINTS

5.1 Primary Endpoint

Safety and tolerability of long-term treatment with ELX/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, pulse oximetry, and spirometry.

5.2 Other Endpoint

Sweat chloride.

6 STUDY DESIGN

6.1 Overall Design

This is a Phase 3, multicenter, open-label study for subjects who transferred from Study 659-105, a Phase 3 Vertex study investigating VX-659/ TEZ/IVA, who meet eligibility criteria (Section 8 in CSP).

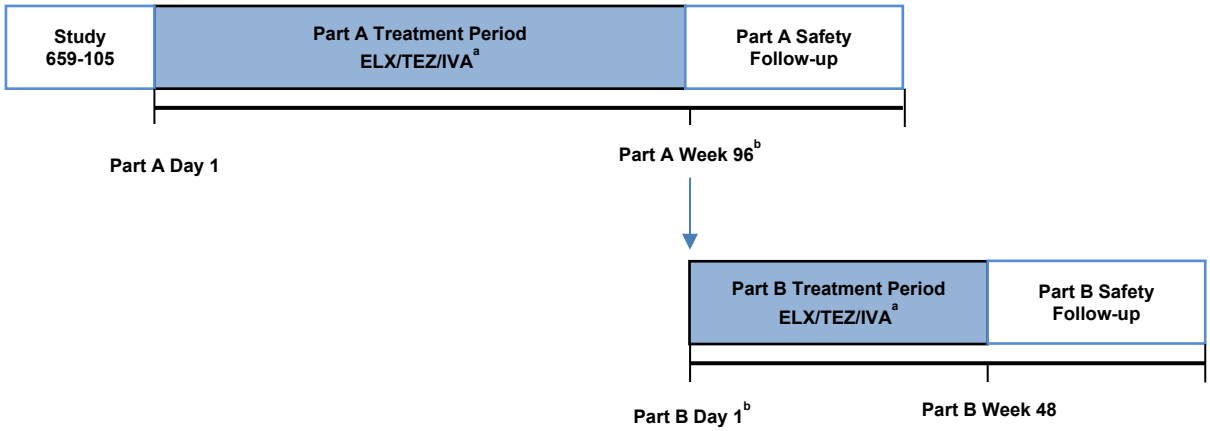
Two separated regional amendments were developed in March 2021. The regional protocol for US and UK was amended to add optional home collected sweat chloride at unscheduled home visit. The study design kept intact as the original one-part design. The regional protocol for Australia, Canada, Spain and Poland was amended to add a Part B, so that subjects in these countries without commercially-available ELX/TEZ/IVA who complete Part A would have the opportunity to participate in Part B for an additional 48 weeks.

A schematic of the study design for the regional amendment of Australia, Canada, Spain and Poland is shown in Figure 6-1. The schematic of the study design for other countries contains only Part A of the Figure 6-1.

All subjects in Parts A and B will receive a TC of ELX/TEZ/IVA at the same dose level as that evaluated in the ELX Phase 3 pivotal trials (ELX 200 mg once daily [qd], TEZ 100 mg once daily [qd], and IVA 150 mg every 12 hours [q12h]). Study drug administration is described in Section 9.6 in CSP.

Study visits and assessments to be conducted for Parts A and B are shown in Table 3-1 and table 3-2, of the CSP respectively. All visits will occur within the windows specified.

Figure 6-1 VX18-445-113 Study Design



ELX: elexacaftor; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor
Note: Figure is not drawn to scale.

[a] All subjects will receive ELX 200 mg qd, TEZ 100 mg qd, and IVA 150 mg q12h.

[b] Subjects whose Part B Day 1 Visit is on the same day as the Part A Week 96 Visit do NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 96 Visit. Subjects whose Part B Day 1 and Part A Week 96 Visits do not coincide must complete all assessments specified for the Part A Week 96 and Part B Day 1 Visits.

For treatment continuity, in countries where ELX/TEZ/IVA is not commercially available (i.e. Australia, Canada, Spain and Poland), an option to return to this study will be offered to subjects who depart this study 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 (Section 8 in CSP) 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

The primary objective of the study is the evaluation of the long-term safety and tolerability of ELX/TEZ/IVA. This is an open-label study that enrolled subjects previously enrolled in Study 659-105 and met the Study 445-113 eligibility criteria.

Over 400 subjects were enrolled. 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 0 events are observed in that PT.

6.3 Randomization

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

6.4 Blinding and Unblinding

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

7 ANALYSIS SETS

The following analysis sets are defined: All Subjects Set and Safety Set.

The **All Subjects Set** for Parts A and B are defined as all subjects who were enrolled (defined as subject having data in the clinical database) in Part A or Part B of this study, respectively. This analysis set will be used for individual subject data listings and disposition summary tables unless otherwise specified.

The **Safety Sets** for Part A and B are defined as all subjects who have received at least 1 dose of study drug in Part A or Part B of this study, respectively. The Safety Set will be used for all safety analyses unless otherwise specified.

8 STATISTICAL ANALYSIS

8.1 General Considerations

In general, data will be summarized by the treatment group in this study.

The precision standards for reporting safety variables are provided in an internal Biometrics document that specifies the programming rules including the precision for derived variables.

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

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

Baseline value, unless otherwise specified, for the long-term safety analysis is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of ELX/TEZ/IVA in Part A of this study.

Baseline of sweat chloride is defined as the most recent non-missing sweat chloride (scheduled or unscheduled) collected before the first dose of VX-659 in VX17-659-102 or VX17-659-103 studies.

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

Relative change from baseline will be calculated as 100% × (post-baseline value – baseline value)/baseline value.

Treatment-emergent (TE) Period for Part A will include the time from the first dose of study drug in Part A to 28 days after the last dose date of the study drug in Part A or to the completion date of study participation in Part A (Section 9.1.5 of the CSP), whichever occurs first.

Treatment-emergent (TE) Period for Part B will include the time from the first dose of study drug in Part B to 28 days after the last dose date of the study drug in Part B or to the completion date of study participation in Part B (Section 9.1.5 of the CSP), whichever occurs first.

The completion date of study participation will be obtained from the end of study page of the eCRF for each part respectively.

For subjects who participate in another qualified Vertex study before completing Study VX18-445-113 and resume participation in Study VX18-445-113, the TE Period for either Part A or B will exclude the time spent in the other study.

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

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

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

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 as no hypothesis test is planned for safety analysis, unless specified otherwise.

8.2 Background Characteristics

8.2.1 Subject Disposition

Part A and Part B

Subject disposition will be summarized for the All Subjects Set for corresponding part.

Number of subjects in the following categories will be summarized:

- All Subjects Set
- Safety Set
- Never dosed

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

- Completed Treatment

- Prematurely discontinued treatment and the reasons for discontinuation
- Completed study
- Prematurely discontinued the study and the reasons for discontinuation
- Departed Study VX18-445-113 to participate in another qualified Vertex study
- Departed Study VX18-445-113 to participate in another qualified Vertex study and returned to VX18-445-113
- Subjects rolled over to Part B (for Part A only).

A listing will be provided by part, for subjects who discontinued treatment or who discontinued study with reasons for discontinuation. A separated listing will be provided by part for subjects who departure from the study.

8.2.2 Demographics and Baseline Characteristics

Part A and Part B

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

Demographic data will include the following:

- Age at baseline (in years)
- Sex (female and male)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Collected per Local Regulations and Other)
- Geographic region (North America, Europe [including Israel and Australia])

Baseline characteristics will include the following:

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

Disease characteristics will include the following:

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

- Prior use of any inhaled hypertonic saline (Yes, No)
- Infection with *Pseudomonas* aeruginosa within 2 years prior to screening visit of VX-659 in VX17-659-102 or VX17-659-103 (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 summarized separately for Parts A and B based on the Safety Set.
Part A and Part B

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

8.2.4 Prior and Concomitant Medications

Prior and concomitant medications will be summarized separately for Parts A and B based on the Safety Set.
Part A and Part B

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

- **Prior medication:** any medication that was administered during the 56 days before the first dose of study drug in the corresponding part. For subjects who enroll in another qualified Vertex study before completing this study and resume participation in this study, any new or changed medication administered after the Departing Visit and prior to the first dose of this study's study drug after resuming participation will also be considered prior medication.
- **Concomitant medication:** medication continued or newly received during the TE Period in the corresponding part.
- **Post-treatment medication:** medication continued or newly received after the TE Period in the corresponding part.

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

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

Prior medications and concomitant medications will be summarized descriptively using frequency tables based on the Safety Set by: 1) preferred name (PN); and 2) Anatomical

Therapeutic Chemical (ATC) level 1, ATC level 2, and PN. All medications will be listed for each subject.

8.2.5 Study Drug Exposure

Exposure summaries will be separated for Parts A and B based on the Safety Set.

Part A and Part B

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

For subjects who enroll in another qualified Vertex study before completing this study and resume participation in this study, time spent in the other study will be excluded.

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 into the following categories: <=24 weeks, >24-<=48 weeks, >48-<=72 weeks, >72-<=96 weeks, >96 weeks for Part A; <=24 weeks, >24-<=48 weeks, >48 weeks for Part B .

Additionally, the total study drug exposure, defined as the sum 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 separately for Parts A and B based on the Safety Set.

Part A and Part B

Study drug compliance will be calculated as: 100 × [1 – (total number of days of study drug interruption) / (duration of study drug exposure in days)]. A study drug interruption on a given day is defined as an interruption of any study drug on that day. For subjects who participate in another qualified Vertex study before completing Study VX18-445-113 and resume participation in Study VX18-445-113, time spent in the other study will be excluded.
Study drug compliance will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized in categories: <80% and ≥80% using frequency tables.

In addition, percentage of tablets taken will be calculated as 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 summary similar to that for study drug compliance will be produced.

8.2.7 Important Protocol Deviations

Important protocol deviation (IPD) will be summarized separately for Parts A and B based on the Safety Set.

Part A and Part B

An IPD is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. A protocol deviation review team will categorize IPDs according to the protocol deviation plan during the study.

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

• Subject was enrolled in the study despite not satisfying one or more inclusion/exclusion criterion

• Subject was less than 80% compliant with study drug for non-safety reasons

• Subject received prohibited concomitant medications

• Subject received the wrong treatment or incorrect doses.

IPDs will be summarized descriptively based on Safety Set for Part A and Part B separately. Additionally, IPDs will be provided in an individual subject data listing based on Safety Set for Part A and Part B separately.

8.3 Efficacy Analysis

Not applicable.

8.4 Safety Analysis

The primary objective of the study is the evaluation of the long-term safety and tolerability of ELX/TEZ/IVA. Safety analysis will be summarized separately for Parts A and B. Part A safety analyses will be based on the TE Period for Part A for subjects in the Safety Set for Part A. Part B safety analyses will be based on the TE Period for Part B for subjects in the Safety Set for Part B. The overall long-term safety profile of study drug will be assessed in terms of the following safety and tolerability endpoints:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., serum chemistry, hematology, coagulation, and urinalysis)
- ECGs
- Vital signs including body weight and BMI
- Pulse oximetry
- Spirometry

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

8.4.1 Adverse Events

Summaries of TEAEs will be provided separately for Parts A and B based on the Safety Set.

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs, or post-treatment AEs for the corresponding part, defined as follows:

- **Pretreatment AE:** any AE that occurred before the first dose date of study drug in the TE Period in the corresponding part. For subjects who enroll in another qualified Vertex study before completing this study and resume participation in this study, AEs that started during participation in another qualified Vertex study and are ongoing at the time of Returning Visit will be flagged as pre-treatment AE.

- **TEAE:** any AE that worsened (either in severity or seriousness) or newly developed at or after the first dose date of study drug in the TE Period in the corresponding part.
- **Post-treatment AE:** any AE that worsened (either in severity or seriousness) or that was newly developed after the TE period in this study in the corresponding part.

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

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

An overview of all TEAEs will be provided with the following categories separately for Parts A and B:

- 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 (discontinuation of any study drugs)
- 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 will be presented separately for Parts A and B:

- 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 separately for Parts A and B 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 or a continuing 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.

Additional summary tables separately for Parts A and B will be presented for TEAEs showing number, percentage of subjects, and the exposure adjusted event rate

- All TEAEs by PT

All AEs, including pretreatment AEs, TEAEs, and post-treatment AEs, will be presented in an individual subject data listing based on the All Subjects Set separately for Parts A and B. 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, with a flag indicating the TEAE status for SAEs and deaths for Parts A and B separately.

8.4.2 Clinical Laboratory Assessments

Summaries of laboratory values will be provided separately for Parts A and B based on the Safety Set.

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 during the TE period of the corresponding part separately for Parts A and B.

The number and percentage of subjects with selected test values meeting at least 1 threshold analysis criterion event during the TE period of the corresponding part will be summarized separately for Parts A and B. The threshold analysis criterion shift from baseline will also be summarized for selected laboratory test values separately for Parts A and B. The threshold analysis criteria are provided in Appendix D.

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

Results of positive urine/serum pregnancy test will be listed in individual subject data listings only separately for Parts A and B. For positive serum pregnancy listing, subjects with serum HCG which are abnormally high will be selected separately for Parts A and B.

In addition, a listing containing individual subject hematology, chemistry, coagulation and urinalysis values will be provided separately for Parts A and B. This listing will include data from both scheduled and unscheduled visits.

8.4.3 Electrocardiogram

Summaries of ECG values will be provided separately for Parts A and B based on the Safety Set.

For the following ECG interval measurements during the TE period of the corresponding part, a summary of observed values and change from baseline values (in msec) will be provided at each visit separately for Parts A and B: RR interval, PR interval, QT interval, 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 during the TE period of the corresponding part will be summarized separately for Parts A and B. The threshold analysis criteria are provided in Appendix D.

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

8.4.4 Vital Signs

Summaries of vital sign values will be provided separately for Parts A and B based on the Safety Set.

For the vital sign measurements during the TE period for the Safety Set for the corresponding part, the observed values and change from baseline values will be summarized at each visit separately for Parts A and B. The following vital signs parameters will be summarized: BMI (kg/m^2), weight (kg), 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 during the TE period for the corresponding part will be summarized separately for Parts A and B. The threshold analysis criteria are provided in Appendix D.

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

8.4.5 Pulse Oximetry

Summaries of pulse oximetry values will be provided separately for Parts A and B based on the Safety Set.

For the percent of oxygen saturation measurements using pulse oximetry during the TE period for the Safety Set for the corresponding part, a summary of observed values and change from baseline values will be provided at each visit separately for Parts A and B.

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 corresponding part will be summarized separately for Parts A and B. The reference range for normal oxygen saturation is specified as >95%, and <=95% for low oxygen saturation.

8.4.6 Physical Examination

No tables/figures/listings will be provided for PE data.

8.4.7 Ophthalmology Examination

Ophthalmology examination results will be provided in a data listing separately for Parts A and B, as applicable.

8.4.8 Spirometry

Summaries of spirometry will be provided separately for Parts A and B based on the Safety Set.

Summary statistics for raw values of the following spirometry measurements i.e. FEV_1 (L), percent predicted FEV_1 (percentage points), FVC (L), percent predicted FVC (percentage points), $FEF_{25-75\%}$ (L/sec), percent predicted $FEF_{25-75\%}$ (percentage points), FEV_1/FVC, percent predicted FEV_1/FVC (percentage points), will be presented at each visit for Part A and Part B separately.

Percent predicted FEV_1 ($ppFEV_1$): the $ppFEV_1$ value is the ratio of FEV_1 (L) and predicted FEV_1 (L), expressed as a percentage. See Appendix F for more details.

[redacted]

8.6 Other Analyses

8.6.1 Sweat Chloride

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

values reported as <10 mmol/L or >160 mmol/L will be considered missing for analysis purposes.

Clinic collected Sweat Chloride data
Clinic collected SwCl values and change from SwCl baseline will be summarized using descriptive statistics by genotype (i.e. F/MF and F/F) at each visit for Part A and B respectively based on the Safety Set.

Home collected Sweat chloride data
Home collected SwCl values will be summarized using descriptive statistics for subjects with valid home collected SwCl values (a subset of approximately 50 subjects). Average will be taken for a subject if the subject has more than 1 valid home collected SwCl values collected at different unscheduled visits. In addition, the clinic collected sweat chloride at the scheduled visits will also be summarized for the same subset of subjects.

9 INTERIM AND DMC ANALYSES

9.1 Interim Analysis

IA may take place at any time during the study at the discretion of the sponsor.

9.2 IDMC Analysis

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

10 REFERENCES

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

11 APPENDICES

Appendix A: Analysis Visit Windows for Safety Assessments

Table 11-1 Analysis Visit Windows for Safety Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2]
Part A			
Spirometry Serum Chemistry Hematology Vital Signs[3] Pulse Oximetry	Baseline Day 15 Week 4 Week 8 Week 16 Week 24 Week 36 Week 48 Week 60 Week 72 Week 84 Week 96 Safety Follow-up[4]	1 15 29 57 113 169 253 337 421 505 589 673 Not applicable	defined in section 8.1 [1, 22] where day 1 is post-dose measurement (22, 43] (43, 85] (85, 141] (141, 211] (211, 295] (295, 379] (379, 463] (463, 547] (547, 631] (631, 687] Use nominal visit
Standard 12-lead ECG	Baseline Day 15 Week 8 Week 24 Week 48 Week 72 Week 96 Safety Follow-up[4]	1 15 57 169 337 505 673 Not applicable	defined in section 8.1 [1, 36] where day 1 is post-dose measurement (36, 113] (113, 253] (253, 421] (421, 589] (589, 687] Use nominal visit
Coagulation	Baseline Week 24 Week 48 Week 72 Week 96 Safety Follow-up[4]	1 169 337 505 673 Not applicable	defined in section 8.1 [1, 253] where day 1 is post-dose measurement (253, 421] (421, 589] (589, 687] Use nominal visit

Table 11-1 Analysis Visit Windows for Safety Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2]
Weight, Height and BMI	Baseline	1	defined in section 8.1
	Week 4	29	[1, 43] where day 1 is post-dose measurement
	Week 8	57	(43, 85]
	Week 16	113	(85, 141]
	Week 24	169	(141, 211]
	Week 36	253	(211, 295]
	Week 48	337	(295, 379]
	Week 60	421	(379, 463]
	Week 72	505	(463, 547]
	Week 84	589	(547, 631]
	Week 96	673	(631, 687]
	Safety Follow-up[4]	Not applicable	Use nominal visit
Sweat Chloride (Clinic collected only)	Baseline	--	defined in section 8.1
	Week 24	169	[1, 421] where day 1 is post-dose measurement
	Week 96	673	(421, 687]
Sweat Chloride (collected at unscheduled home visits)	Home SwCl collection visit 1	Not applicable	Use nominal visit[5]
	Home SwCl collection visit 2	Not applicable	Use nominal visit[5]
Part B			
Spirometry Serum Chemistry Hematology Vital Signs[3] Weight, Height and BMI Pulse Oximetry	Baseline	--	defined in section 8.1
	Part B Week 12	85	[1, 127] where day 1 is post-dose measurement
	Part B Week 24	169	(127, 211]
	Part B Week 36	253	(211, 295]
	Part B Week 48	337	(295, 351]
	Part B Safety Follow-up[4]	Not applicable	Use nominal visit
Standard 12-lead ECG	Baseline	--	defined in section 8.1
	Part B Week 12	85	[1, 127] where day 1 is post-dose measurement
	Part B Week 24	169	(127, 253]
	Part B Week 48	337	(253, 351]
	Part B Safety Follow-up[4]	Not applicable	Use nominal visit
Coagulation	Baseline	--	defined in section 8.1
	Part B Week 24	169	[1, 253] where day 1 is post-dose measurement
	Part B Week 48	337	(253, 351]
	Part B Safety Follow-up[4]	Not applicable	Use nominal visit
Sweat Chloride[5]	Baseline	--	Defined in section 8.1
	Part B Week 24	169	[1, 253] where day 1 is post-dose measurement
	Part B Week 48	337	(253, 351]

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 except for SwCl collected at unscheduled home 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. If the latest measurement cannot be determined, then unscheduled visit will be selected.

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

1. Scheduled measurement will be treated as pre-dose observation.
2. Unscheduled measurement will be treated as post-dose observation.

[4] For safety Assessment, Safety Follow-up analysis visit will be based on nominal Safety Follow-up visit. If a subject doesn't have a nominal Safety Follow-up visit but has an ETT visit with study day >687 for Part A or >351 for Part B, then the ETT visit will be mapped into Safety Follow-up analysis visit for the corresponding part.

[5] If one subject has multiple home collected SwCl samples at different unscheduled visits, the assignment of the visits will be based on chronological order.

Derived Variables for each part:

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) from the Vital Signs (VS) page at the Day 1 Visit 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 days + age at informed consent (in days)]/365.25.

2. Missing first dose date or last dose date

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

   If the last dose date of study drug is not available and there is no data to indicate that the subject discontinued treatment, the data cutoff date will be used instead.

   If the subject discontinued treatment and 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 data cutoff date.

3. Electrocardiogram:

   Baseline is defined in Section 8.1. If multiple ECG measurements are obtained on the same calendar day during the TE 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

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

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

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

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

P: Prior; C: Concomitant; A: Post

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

Appendix C: Imputation Rules for Missing AE dates

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

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

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

Imputation rules for partial AE end date are defined below:

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

Appendix D: 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 - ≤ 20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
AST	>ULN - ≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >8x - ≤ 20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
ALT or AST	(ALT>ULN - ≤ 3xULN) or (AST>ULN - ≤ 3xULN) (ALT>3x - ≤ 5xULN) or (AST>3x - ≤ 5xULN) (ALT>5x- ≤ 8xULN) or (AST>5x - ≤ 8xULN) (ALT>8x - ≤ 20xULN) or (AST>8x - ≤ 20xULN) ALT>20xULN or AST> 20 xULN	FDA DILI Guidance
Alkaline Phosphatase	>ULN - ≤ 1.5xULN >1.5 – ≤ 2.5 xULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>ULN - ≤ 1.5xULN >1.5 – ≤ 2xULN >2 – ≤ 3xULN >3 – ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
Direct Bilirubin	>ULN - ≤ 1.5xULN >1.5 – ≤ 2xULN >2 – ≤ 3xULN >3 – ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
Indirect Bilirubin	>ULN - ≤ 1.5xULN >1.5 – ≤ 2xULN >2 – ≤ 3xULN >3 – ≤ 10xULN >10xULN	FDA DILI Guidance Jul 2009.
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.

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

Parameter	Threshold Analysis	Comments
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	FDA DILI Guidance Jul 2009.
GGT	>ULN - ≤ 2.5xULN >2.5 – ≤ 5.0xULN >5.0 – ≤ 20.0xULN >20.0xULN	CTCAE grade 1-4
Clinical Chemistry (NON-LFT)		
Albumin	<LLN - ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>ULN - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Creatinine	>ULN - ≤ 1.5xULN >1.5 - ≤ 3.0xULN >3.0 - ≤ 6.0xULN >6.0xULN	CTCAE grades 1-4
Lipase	>ULN - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
Creatine Kinase	>ULN - ≤ 2.5 x ULN >2.5 - ≤ 5 x ULN >5 - ≤ 10x ULN >10 x ULN	CTCAE grades 1-4
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 11-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

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 - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN	CTCAE grade 1-3

Table 11-4 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 11-5 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 11-5 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		To be applied to any kind of QT correction formula.
Borderline	>450 ms and <500ms (Male); >470 ms and <500ms (Female)	
Prolonged*	≥500 ms	
Additional	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 11-6 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
Pulse Rate	Same as above in ECG category	
SBP increased		809/770 analyses
	>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	
SBP decrease		Per HV grade 1, 3, plus shift change
	<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	

Table 11-6 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

Appendix E: Adverse Events of Special Interest

Table 11-7 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	Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash vesicular, Rash pruritic, Rash follicular, Rash pustular, Nodular rash, Drug eruption, Fixed eruption, Urticaria, Urticaria papular, Urticaria vesiculosa, Urticarial dermatitis, Rash morbilliform, Rash papular, Rash papulosquamous, Rash rubelliform, Rash scarlatiniform , Drug hypersensitivity, Type IV hypersensitivity reaction, Dermatitis, Dermatitis atopic, Epidermolysis, Skin toxicity, Dermatitis allergic, Dermatitis exfoliative, Dermatitis exfoliative generalised, Erythema multiforme, Exfoliative rash, Mucocutaneous rash, Acute generalised exanthematous pustulosis, Cutaneous vasculitis, Urticarial vasculitis, Dermatitis bullous, Drug reaction with eosinophilia and systemic symptoms, Epidermal necrosis, Oculomucocutaneous syndrome, Skin exfoliation, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, Perioral dermatitis, Vasculitic rash, Immune-mediated dermatitis, Penile rash, SJS-TEN overlap, Erythrodermic atopic dermatitis, Scrotal rash

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

Appendix F: 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 July 1, 2019].

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 July 1, 2019].

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 July 1, 2019].

Data handling rule for spirometry is as follows:

- Input age with at least 2 decimal place
- Use height at Day 1 Visit regardless if height is collected at other study visits for subjects whose age at informed consent is >21 years. For subjects with age at informed consent is <=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.