1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX19-864-101, Version 1.0 (Interim and Final Analysis)

A Phase 2, Randomized, Double-blind, Placebo-controlled Study of the Efficacy and Safety of VX-864 in *PiZZ* Subjects

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Version: 1.0
Version Date of SAP: 11 May 2021

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4 INTRODUCTION

This statistical analysis plan (SAP) describes the efficacy, safety, [redacted] 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. [redacted]

All analysis outputs (tables, figures, listings, and datasets) will be generated using SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA).

The SAP (Methods) will be finalized and approved before the clinical database lock. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP prior to the clinical database lock. Any revisions made to the SAP after the clinical database lock will be documented in the clinical study report for this study.

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

5 STUDY OBJECTIVES

5.1 Primary Objectives

- To evaluate the efficacy of VX-864 in *PiZZ* subjects as measured by plasma functional alpha-1 antitrypsin (AAT) levels
- To evaluate the safety and tolerability of VX-864 in *PiZZ* subjects

5.2 Secondary Objectives

- To evaluate the efficacy of VX-864 in *PiZZ* subjects as measured by plasma antigenic AAT levels
- To evaluate the pharmacokinetics (PK) of VX-864 in *PiZZ* subjects

[redacted]

[redacted]

6 STUDY ENDPOINTS

6.1 Primary Endpoints

- Change from baseline in plasma functional AAT levels at Day 28
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry

6.2 Secondary Endpoints

- Change from baseline in plasma antigenic AAT levels at Day 28
- PK parameters of VX-864 derived from plasma concentration-time data

[redacted]

7 STUDY DESIGN

7.1 Overall Design

This is a Phase 2, randomized, double-blind, placebo-controlled study of VX-864. Schematics of the study design are shown in Figure 7-1 and Figure 7-2.

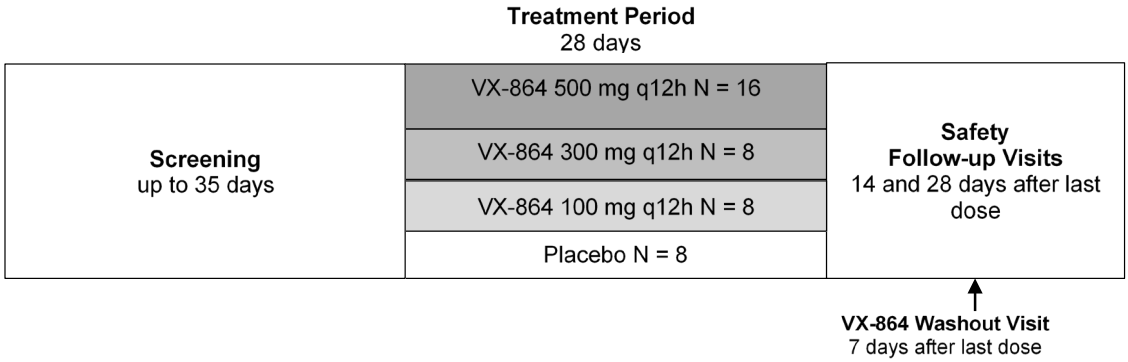
Approximately 40 subjects in total with the *PiZZ* genotype and antigenic AAT levels <8 µM at screening will be randomized to VX-864 or placebo 2:1:1:1 to VX-864 500 mg q12h, VX-864 300 mg q12h, VX-864 100 mg q12h, or placebo.

Of these, approximately 20 subjects will be randomized 2:2:1 to VX-864 500 mg q12h, VX-864 300 mg q12h, or placebo first. The remaining subjects (approximately 20) will be randomized

2:2:1 to VX-864 500 mg q12h, VX-864 100 mg q12h, or placebo. Randomization will be stratified by post-bronchodilator percent predicted forced expiratory volume in 1 second ($ppFEV_1$) obtained either during the Screening Period or from a historical post-bronchodilator $ppFEV_1$ value measured within 1 year before screening (<50% versus ≥50%).

Screening assessments for subjects who have never been on augmentation therapy are listed in Table 3-1 of the protocol. Screening assessments for subjects who have been on augmentation therapy at any time are listed in Table 3-2 of the protocol. Treatment Period assessments for all subjects are listed in Table 3-3 of the protocol.

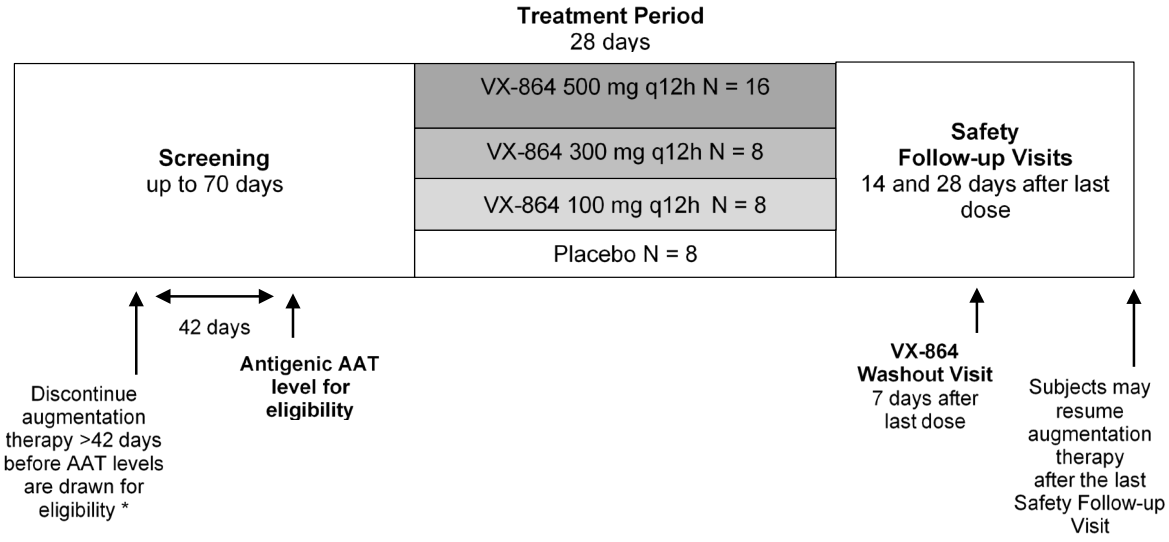
Figure 7-1 Schematics of Study Design for Subjects Who Have Never Been on Augmentation Therapy



AAT: alpha-1 antitrypsin; N: number of subjects; q12h: every 12 hours

Notes: Figure is not drawn to scale. Subject numbers include subjects who have never been on augmentation therapy and subjects who have been on augmentation therapy at any time. Antigenic AAT levels must be drawn to confirm eligibility and sent to the central laboratory; results must be obtained and confirmed to be <8 μM before randomization. Once antigenic AAT levels have been confirmed to meet this eligibility criterion, randomization and Day 1 can occur any time within the remaining screening window. **Sites should allow at least 14 days for sample processing and antigenic AAT level result reporting.**

Figure 7-2 Schematics of Study Design for Subjects Who Have Been on Augmentation Therapy at Any Time



AAT: alpha-1 antitrypsin; N: number of subjects; q12h: every 12 hours

Notes: Figure is not drawn to scale. Subject numbers include subjects who have never been on augmentation therapy and subjects who have been on augmentation therapy at any time. Subjects must discontinue augmentation therapy >**42 days** before antigenic AAT levels are drawn and **sent to the central laboratory** to confirm eligibility; results must be confirmed to be <8 μM before randomization. Once antigenic AAT levels have been confirmed to meet this eligibility criterion, randomization and Day 1 can occur any time within the remaining screening window. **Sites should allow at least 14 days for sample processing and antigenic AAT level results reporting.** Subjects can resume augmentation therapy after completion of assessments at the last Safety Follow-up Visit.

*Blood samples will be obtained for antigenic and functional AAT levels at the same time that the other screening laboratory assessments are performed. If the subject received the last dose of augmentation therapy >42 days prior, this sample can be used to measure antigenic AAT level for eligibility. If samples are obtained ≤42 days after the last dose of augmentation therapy, another sample **must** be drawn >42 days after the last dose of augmentation therapy and sent to the central laboratory to confirm eligibility.

7.2 Sample Size and Power

Subjects will be randomized 2:1:1:1 to receive VX-864 500 mg q12h (n = 16), VX-864 300 mg q12h (n = 8), VX-864 100 mg q12h (n = 8), or placebo (n = 8).

Assuming 10% of the randomized subjects have a missing value at Day 28, this sample size provides adequate precision to estimate the absolute plasma functional AAT levels at Day 28 for the VX-864 500 mg q12h dose group.

Information regarding the sample size assessments is provided below.

[redacted]

7.3 Randomization

Refer to Section 9.3 of the CSP for details.

7.4 Replacement

Refer to Section 9.11 of the CSP for details.

7.5 Blinding and Unblinding

Refer to Section 10.7 of the CSP for details.

8 ANALYSIS SETS

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

8.1 All Subjects Set

The **All Subjects Set** will include all subjects who were 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.

8.2 Full Analysis Set

The **FAS** will include all randomized subjects who received at least 1 dose of study drug. The FAS will be used to summarize subject demographics and background characteristics, and for all efficacy analyses, unless otherwise specified. Subjects will be analyzed according to the treatment to which they were randomized.

8.3 Safety Set

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

9 STATISTICAL ANALYSIS

9.1 General Considerations

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

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

ECGs, the baseline value will be defined as the average of the non-missing pre-dose measurements (triplicate) collected before the first dose of study drug. For subjects who have ever been on augmentation therapy at any time, only functional and antigenic AAT levels collected >42 days after the last dose of augmentation therapy can be used to define baseline values. For antigenic AAT levels, only the screening results obtained from the on-treatment assay can be used to define baseline values if the Day 1 pre-dose results are missing.

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

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

Treatment-emergent (TE) Period will include the time period starting from the date of the first dose of study drug to either (1) Safety Follow-up Visit 28 days after the last dose of study drug, (2) Early Termination of Treatment (ETT) Visit if it replaces the Safety Follow-up Visit 28 days after the last dose of study drug, or (3) 28 days after the last dose date for subjects who do not have a Safety Follow-up Visit 28 days after the last dose or an equivalent ETT.

[redacted]

Unscheduled visits: Data obtained from unscheduled visits will be included in the analysis as follows:

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

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

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

Additional considerations:

- For all model-based assessments, a dose group will only be included if ≥3 subjects have non-missing data available.
- An individual subject data listing will be provided for subject visits impacted by COVID-19.

- If appropriate and if needed, additional analysis of the functional and antigenic AAT endpoints may be performed excluding any AAT measurements influenced by a PEx and/or a COVID-19 vaccination.

All individual subject data will be presented in individual subject data listings based on the All Subjects Set.

9.2 Background Characteristics

9.2.1 Subject Disposition

The disposition summary will be provided by treatment group and overall.

The number of subjects, based on the All Subjects Set, in the following disposition categories, will be summarized:

- All Subjects Set
- Full Analysis Set
- Safety Set
- Randomized
- Randomized but not dosed

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

- Completed treatment
- Discontinued treatment and the reason for discontinuation from treatment
- Completed study
- Discontinued study and the reason for discontinuation from study

9.2.2 Demographics and Baseline Characteristics

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

Demographic data will include the following:

- Age (in years)
- Sex (female and male)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)

- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, and Not Collected per Local Regulations)

Baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Prior Augmentation Therapy (Yes, No)
- Smoking History (Yes, No)
- $ppFEV_1$ category determined during the Screening Period or from historical data (< 50%, ≥50%)
- $ppFEV_1$ obtained during the Screening Period or from historical data (%)
- FEV_1 obtained during the Screening Period or from historical data (L)
- FVC obtained during the Screening Period or from historical data (L)
- Ratio of FEV_1 and FVC obtained during the Screening Period or from historical data (%)
- Functional AAT level (µM)
- Antigenic AAT level (µM)

9.2.3 Medical History

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized descriptively based on the FAS by MedDRA system organ class (SOC) and preferred term (PT). This summary will be provided by treatment group and overall.

9.2.4 Prior and Concomitant Medications

Medications will be coded using the World Health Organization-Drug Dictionary (WHODrug) and categorized as the following for the purposes of analysis:

Prior medication: Medication that started before the first dose of study drug

Concomitant medication: Medication continued or newly received during the TE Period

Post-treatment medication: Medication continued or newly received after the TE Period

A given medication may be classified as a prior medication, a concomitant medication, a post-treatment medication, or more than one of these categories.

If a medication start date is on or after the first dose date of study drug, then the medication will be classified as a concomitant medication regardless of whether the medication end date is missing or not. If a medication end date is before the first dose date of study drug, then the medication will be classified as a prior medication regardless of whether the medication start date is missing or not. Note that a medication that started before the first dose of study drug and continued after the first dose will be classified as a prior medication and separately as a concomitant medication.

If a medication has a missing or partially missing start/end date and it cannot be determined whether it was taken before the first dose of study drug, or concomitantly, it will be classified as a prior and a concomitant medication.

Missing or partial dates will be imputed for medications. Details for imputing missing or partial start and/or stop dates of medications are described in Appendix B.

Prior and post-treatment medications will not be summarized but will only be listed. Concomitant medications will be summarized based on the FAS by PT. This summary will be provided by treatment group and overall across the VX-864 treatment groups. Bronchodilator usage will also be listed.

Prior, concomitant, and post-treatment non-pharmacological therapy will be listed.

9.2.5 Study Drug Exposure and Compliance

Study drug exposure (in days) will be calculated as (last date of dosing – first date of dosing) + 1, regardless of study drug interruption, and will be summarized descriptively based on the Safety Set by treatment group and overall. It will also be summarized in categories: $\leq$ 7 days, $>$ 7 to $\leq$ 14 days, $>$ 14 to $\leq$ 21 days, $>$ 21 to $\leq$ 28 days, and $>$ 28 days, using counts and percentages.

Study drug compliance will be calculated as 100 $\times$ [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 any interruption of the study drug on that day. A study drug interruption that continues through the end of study participation (i.e., subject does not resume study drug before the end of study participation) will not be included in the compliance calculation. Study drug compliance will be summarized descriptively based on the FAS by treatment group and overall. It will also be summarized in categories: <80% and $\geq$80%, using counts and percentages.

9.2.6 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's

rights, safety, or well-being. IPD rules will be developed and finalized before clinical database lock. IPDs will be identified by the PD review team according to the Protocol Deviation Plan.

IPDs will be summarized descriptively based on the FAS by treatment group and overall.

9.3 Efficacy Analysis

All efficacy analyses described in this section will be based on the FAS, unless otherwise specified. Subjects will be analyzed according to the treatment to which they were randomized.

9.3.1 Analysis of Primary Efficacy Variable

9.3.1.1 Definition of Primary Efficacy Variable

The primary efficacy variable is the change from baseline in plasma functional AAT levels at Day 28.

9.3.1.2 Primary Analysis

The primary analysis of the primary efficacy variable includes data from VX-864 treatment groups and the placebo group. The primary comparison consists of the pairwise comparison between each dose of VX-864 and placebo.

[redacted]

The primary analysis will be based on a mixed-effects model for repeated measures (MMRM) with change from baseline at Days 7, 14, and 28 as the dependent variable. The MMRM model will include the treatment group, visit, and treatment-by-visit interaction as fixed effects. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, a compound symmetry covariance structure will be used instead. 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. Conditional on the observed data and covariates, missing data will be assumed to be missing at random; consequently, no imputation of missing data will be performed.

The primary result obtained from the model will be the estimated treatment difference between each VX-864 treatment group in the model and the placebo group at Day 28. The adjusted means with 2-sided 95% confidence intervals and 2-sided *P* values will be provided. In addition, the estimated treatment differences, obtained from the model, between each VX-864 treatment group

in the model and the placebo group at each post-baseline visit will be provided, along with 2-sided 95% confidence intervals and 2-sided *P* values.

The observed values and change from baseline of functional AAT levels will also be summarized descriptively by treatment group at each visit.

[redacted]

9.3.2 Analysis of Secondary Efficacy Variable

9.3.2.1 Definition of Secondary Efficacy Variable

The secondary efficacy variable is the change from baseline in plasma antigenic AAT levels at Day 28.

9.3.2.2 Analysis Method

The analysis of the secondary efficacy variable includes data from VX-864 treatment groups and the placebo group. [redacted]

Analysis of the secondary efficacy variable will be based on an MMRM similar to the primary analysis of the primary efficacy variable, with change from baseline in plasma antigenic AAT levels at Days 7, 14, 28 as the dependent variables and the treatment group, visit, and treatment-by-visit interaction as fixed effects. The adjusted means and the estimated treatment differences obtained from the model between each VX-864 treatment group in the model and the placebo group at Day 28, as well as at each post-baseline visit, will be provided, with 2-sided 95% confidence intervals and 2-sided *P* values.

The observed values and change from baseline of the antigenic AAT levels will be summarized descriptively by treatment group at each visit.

[redacted]

9.3.3 Multiplicity Adjustment

There is no multiplicity adjustment for the pairwise comparisons between each dose of VX-864 and placebo.

9.4 Safety Analysis

Safety is one of the primary objectives of this study. All safety analyses will be performed based on the Safety Set. Subjects will be analyzed according to the treatment they actually received in the treatment period. For subjects receiving more than one dose level, the treatment allocation will be the highest dose level.

The overall safety profile of VX-864 will be assessed in terms of the following safety endpoints:

- Incidence of treatment emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., hematology, serum chemistry, coagulation, and urinalysis)
- Standard 12-lead ECG outcomes
- Vital signs
- Pulse oximetry

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

9.4.1 Adverse Events

AEs will be coded using MedDRA. The number and percentage of subjects experiencing an AE will be summarized by the MedDRA SOC and PT. AEs will be classified as pretreatment or treatment-emergent as follows:

Pretreatment AEs: AEs that occurred before the first dose of study drug

Treatment-emergent AEs: AEs that worsened or started on or after the first dose date of study drug through the end of the TE Period

Post-treatment AEs: AEs that worsened or started after the TE Period

For AEs with completely missing or partial start dates, if there is no clear evidence that the AEs started before or after the first dose of study drug, the AEs will be classified as TEAEs.

Imputation rules for missing or partial AE start dates are defined as Appendix C.

AE summary tables will be presented for only TEAEs by treatment group (including placebo and each VX-864 dose group) and overall across the VX-864 treatment groups, and will include the following:

- Overview of TEAEs
- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to death
- Serious TEAEs
- Related TEAEs
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption

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. Only the maximum severity level will be presented in the severity summaries, and the strongest relationship level in the relationship summaries.

In addition, listings containing individual subject-level AE data for all deaths, SAEs, treatment discontinuations, and treatment interruptions will be provided separately.

9.4.2 Clinical Laboratory

All statistical analyses of laboratory values will be performed using SI units. For treatment-emergent laboratory measurements, the observed values and change from baseline values of the continuous hematology, chemistry, and coagulation results will be summarized by treatment group at each visit.

The number and percentage of subjects with chemistry, hematology and coagulation values meeting threshold analysis criteria during the TE period will be summarized by treatment group. The threshold analysis criterion shift from baseline will also be summarized descriptively. [redacted]

In addition, listings containing individual subject hematology, chemistry, and coagulation values outside the reference ranges during the TE Period(s) will be provided. These listings will include data from scheduled and unscheduled visits.

Results of urinalysis and the serum pregnancy test will be presented in individual subject data listings only.

9.4.3 Electrocardiogram

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

The number and percentage of subjects meeting threshold analysis criteria during the TE Period will be summarized by treatment group. [redacted]

[redacted]

Since ECGs are performed in triplicate, the mean of the ECGs will be used as the ECG value for summaries of observed values and change from baseline values, and all reported ECGs will be used to conduct threshold analyses.

9.4.4 Vital Signs

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

The number and percentage of subjects meeting threshold analysis criteria during the TE Period will be summarized by treatment group. [redacted]

9.4.5 Pulse Oximetry

For the treatment-emergent pulse oximetry measurements of the percentage of oxygen saturation, the observed values and change from baseline values will be summarized by treatment group at each visit.

9.4.6 Spirometry

Spirometry results, including FVC (L), FEV_1 (L), and percent predicted FEV_1 ($ppFEV_1$, %), will be presented in an individual subject data listing only. The guideline for calculating $ppFEV_1$ is provided in Appendix E.

9.4.7 Physical Examination

Physical examination (PE) results will be presented in an individual subject data listing only.

[redacted]

10 INTERIM AND IDMC ANALYSES

10.1 Interim Analysis (Optional)

Interim analyses (IA) may be performed at any time at the discretion of the sponsor for internal decision-making. Interim analyses will be performed and reviewed by an unblinded Vertex team not involved in the conduct of the study.

Interim analyses will be based on all data included in the IA data cuts.

10.1.1 General Consideration

General considerations, reporting conventions, and analysis methods specified for the final analysis apply to the IA, unless otherwise specified.

For the IA, **the treatment-emergent (TE) period** will include the time period starting from the date of the first dose of study drug to either (1) Safety Follow-up Visit 28 days after the last dose of study drug, (2) ETT Visit if it replaces the Safety Follow-up Visit 28 days after the last dose of study drug, (3) 28 days after the last dose date for subjects who do not have a Safety Follow-up Visit 28 days after the last dose or an equivalent ETT, or (4) the IA data cut date if subjects have not completed or discontinued the study at the time of the IA data cut.

10.1.2 Background Characteristics

Refer to section 9.2 for the summary of background characteristics for the IA. In addition, "treatment ongoing" and "study ongoing" will be possible disposition categories for the IA.

10.1.3 Efficacy Analysis

Descriptive statistics for the primary and secondary efficacy variables only will be presented for the IA.

10.1.4 Safety Analysis

Refer to Section 9.4 for the safety analysis for the IA.

[redacted]

10.2 Independent Data Monitoring Committee Analysis

Not applicable.

11 REFERENCES

Not applicable.

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

Missing or partial dates will be imputed for medications. The algorithm for a missing or partial start date is:

a. If day is missing, use the first day of the month;

b. If month is missing, use January (1 January if day is also missing);

c. If year is missing, no imputation is conducted.

The algorithm for a missing or partial end date is:

a. If day is missing, use the last day of the month;

b. If month is missing, use December (31 December if day is also missing);

c. If year is missing, no imputation is conducted.

The missing data algorithms will be reviewed to ensure their accuracy. For example, after imputation, the end date will not precede the start date.

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

Table 12-2 Categorization of a Medication

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

A: Post-treatment; C: Concomitant; P: Prior

Imputation of missing and/or partial dates for non-pharmacological treatments/procedures will follow the same imputation rule.

Appendix C: Imputation Rules for Missing AE Dates

Imputation rules for missing or partial AE start dates are defined below. If the imputed AE start date is before the study 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 AE start year and month are the same as that for the first dose date, then:
    - If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of the first dose date;
    - Otherwise, impute the AE start day as 1.
  - Otherwise, impute the AE start day as 1.

  Compare the imputed AE start date with the TE period to determine whether the AE is a pretreatment AE or TEAE.
- **If Day and Month of AE start date are missing:**
  - If AE start year = first dose year, then:
    - If the full (or partial) AE end date is NOT before the first dose date or the AE end date is missing, then impute the AE start month and day as the month and day of the first dose date;
    - Otherwise, impute the AE start month as January and the day as 1.
  - Otherwise, impute the AE start month as January and the day as 1.

  Compare the imputed AE start date with the TE period to determine whether the AE is a pretreatment AE or TEAE.
- **If Year of AE start date is missing:**

  If the year of AE start date is missing or the AE start date is completely missing, then query the site with no imputation. Compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date, then the AE should be considered as a pretreatment AE. Otherwise, the AE will be considered as a TEAE.

A missing or partially missing AE end date will not be imputed.

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

The percent predicted value will be calculated for parameters of FEV$_1$, using the Quanjer GLI-2012 Regression Equations and Lookup Tables.

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

Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Quanjer GLI-2012 Regression Equation and Lookup Tables (Version 7 April 2013). Global Lung Function Initiative. [online] Available at: https://www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools/it-engineers-and-manufacturers.aspx [Accessed 16 August 2020].

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: https://www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools/it-engineers-and-manufacturers.aspx [Accessed 6 October 2020].

Sanja Stanojevic. GLI-2012 - SAS Macro (Version 2, 7 April 2013). Global Lung Function Initiative. [online] Available at: https://www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools/sas-macro/ [Accessed 16 August 2020].

Data handling rules for the ppFEV$_1$ calculation are as follows:

- Input age with at least 2 decimal places.
- For historical spirometry, use the height at the time of the FEV$_1$ measurement to calculate ppFEV$_1$; for spirometry performed on or after informed consent, use height at screening for the calculation.
- For race, map the CRF-reported Black or African American to Black; all other races in CRF (except White) are mapped to Other. Multiple selections for race in CRF are also mapped to Other. White is a reference race in the equations and assumes values of zero for all race coefficients in the GLI equations.