1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX22-864-108, Version 2.0

A Phase 2, Open-label Study Evaluating Efficacy and Safety of VX-864 in Subjects With Alpha-1 Antitrypsin Deficiency Who Have the PiZZ Genotype, Over 48 Weeks

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3 MODIFICATIONS

3.1 Modifications to the Approved Clinical Study Protocol

Not applicable.

3.2 Modifications to the Approved Statistical Analysis Plan

Not applicable.

3.3 Modifications to the Approved IDMC Charter

Not applicable.

4 INTRODUCTION

This statistical analysis plan (SAP) describes the efficacy, safety, tolerability 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 approved eCRF completion guidelines. This SAP also documents analyses not specified in the protocol, which will provide supportive information for the scientific understanding of the drug entity.

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.

5 STUDY OBJECTIVES

5.1 Primary Objectives

- To evaluate the efficacy of VX-864 on blood levels of functional alpha-1 antitrypsin (AAT) in individuals with the PiZZ genotype

5.2 Secondary Objectives

- To evaluate the efficacy of VX-864 on blood levels of antigenic AAT in individuals with the PiZZ genotype
- To evaluate the efficacy of VX-864 on blood levels of Z-polymer in individuals with PiZZ genotype
- To evaluate the efficacy of VX-864 on liver Z-polymer in individuals with the PiZZ genotype (in Group B only)
- To evaluate the safety and tolerability of VX-864 in individuals with the PiZZ genotype

[redacted]

6 STUDY ENDPOINTS

6.1 Primary Endpoints

- Change from baseline in blood levels of functional AAT at Week 48

6.2 Secondary Endpoints

- Change from baseline in blood levels of functional AAT over time
- Change from baseline in blood levels of antigenic AAT over time
- Change from baseline in blood levels of Z-polymer over time
- Change from baseline in Z-polymer accumulation in the liver over time (in Group B only)
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, standard 12-lead ECGs, and vital signs

[redacted]

[redacted]

7 STUDY DESIGN

7.1 Overall Design

This is a Phase 2, open-label, multicenter study. Approximately 20 subjects with the PiZZ genotype will be enrolled. Groups A and B will enroll approximately 10 subjects each. All subjects will receive VX-864 500 mg every 12 hours (q12h) for 48 weeks. Figure 7-1 displays the study design.

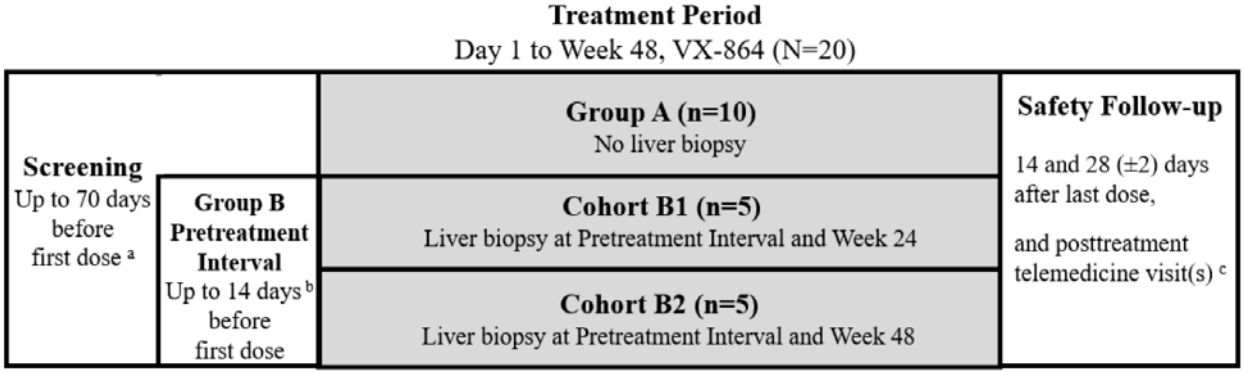
Group A subjects will not have a liver biopsy.

Subjects in Group B will have 2 liver biopsies performed over the course of the study. All liver biopsies will be performed percutaneously. All subjects in Group B (approximately 10 subjects) will have a liver biopsy during the Pretreatment Interval (Figure 7-1). Approximately 5 subjects (Group B1) will have a second liver biopsy at Week 24. Approximately 5 subjects (Group B2) will have a second liver biopsy at Week 48.

The pretreatment liver biopsy must be performed at least 7 days before Day 1 dosing, after all eligibility criteria have been met. Local laboratory hematology and coagulation results must be collected and reviewed by investigator within approximately 48 hours prior to the liver biopsy being performed. The Week 24 and Week 48 liver biopsies will be performed 3 hours (±30 minutes) postdose relative to the morning dose.

The Safety Follow-up Visits are required for all subjects. For subjects who terminate their participation early, the ETT visit, which may be conducted at the site or by telephone or video interview, replaces the Day 28 Safety Follow-up Visit, if the ETT Visit occurs 3 weeks or later following the last dose of study drug. All subjects may also consent to the posttreatment Telemedicine Visit(s) following final dose of study drug, to monitor for development of AEs of rash (for up to 6 months) and to monitor any ongoing AEs of rash (for up to 6 months following resolution of AEs of rash; see Protocol Section 9.1.6).

Figure 7-1 VX22-864-108 Study Design



n: size of subsample; N: number of subjects
Notes: Figure is not drawn to scale. Figure is not drawn to scale.

[a] In subjects not requiring augmentation therapy washout, the Screening Period will be up to 28 days. In subjects requiring augmentation therapy washout, the Screening Period will be up to 70 days.

[b] Day -14 to Day -7; pretreatment liver biopsy must be performed at least 7 days before Day 1 dosing.

[c] There will be no further dosing in this study as of 25 September 2023. All subjects may consent to the posttreatment Telemedicine Visit(s) following final dose of study drug, to monitor for development of AEs of rash (for up to 6 months) and monitor any ongoing AEs of rash (for up to 6 months following resolution of AEs of rash; see Protocol Section 9.1.6).

[redacted]

7.3 Randomization

Not applicable.

7.4 Replacement

Subjects who withdraw or are withdrawn for non-safety reasons during the study drug treatment period may be replaced at Vertex's discretion. Refer to Section 9.10 of the CSP for more 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 (SS).

8.1 All Subjects Set

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

8.2 Full Analysis Set

The **Full Analysis Set (FAS)** is defined as all enrolled subjects who have received at least 1 dose of study drug. The FAS will be used to summarize background characteristics and for all efficacy analyses unless otherwise specified.

8.3 Safety Set

The **Safety Set (SS)** is defined as all subjects who have received at least 1 dose of study drug. The SS will be used for all safety analyses unless otherwise specified.

9 STATISTICAL ANALYSIS

9.1 General Considerations

The Schedule of Assessments is provided in Section 3 of CSP. 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, 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 pretreatment measurements (triplicate) on Day 1. For subjects who have ever been on augmentation therapy at any time, only functional and antigenic AAT levels collected during screening >42 days after the last dose of augmentation therapy can be used to define baseline values.

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

Treatment-emergent (TE) Period will include the time from the first dose of study drug to 28 days after the last dose of study drug or to the completion of study participation (as defined in Section 9.1.8 of CSP), whichever occurs first.

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

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 TE period, and maximum and minimum change from baseline values during 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.

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

Disposition summary will be provided by 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
- Enrolled but not dosed

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

- Completed treatment
- Discontinued treatment and the reason for discontinuation from treatment
- Completed study (i.e., completed Safety Follow-Up Visit or Post-treatment Telemedicine Visit)
- Discontinued the study and the reason for discontinuation from study

The corresponding data listing will also be provided.

9.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized based on the FAS by 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 [Northeast Asian, Southeast Asian, Other Asian, Asian, Region Not Reported], 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% and <80, ≥80%)
- 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)
- Blood Z-polymer level (mg/L)
- Liver Z-polymer level (mg/L) (Group B only)

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 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 purpose 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 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 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 group and overall.

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 group and overall. It will also be summarized in categories: $\leq$ 7 days, $>$ 7 to $\leq$ 28 days, $>$ 28 days to $\leq$ 6 weeks, $>$ 6 to $\leq$ 12 weeks, $>$ 12 to $\leq$ 24 weeks, $>$ 24 to $\leq$ 48 weeks, and $>$ 48 weeks, using counts and percentages.

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 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 group and overall. It will also be summarized in categories: <80% and ≥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 the 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 group and overall.

9.3 Efficacy Analysis

All efficacy analyses described in this section will be based on the FAS, unless otherwise specified.

9.3.1 Analysis of Primary Efficacy Variable

The primary efficacy endpoint is the change from baseline in blood levels of functional AAT at Week 48.

According to CSP (V2.0), [redacted]

9.3.2 Analysis of Secondary Efficacy Variables

In this analysis, if the measured functional AAT levels are below the lower limit of quantification (LLOQ) of 2.77 µM, the LLOQ value will be imputed for analysis purposes; if the measured functional AAT levels are above the upper limit of quantification (ULOQ) of 25.6 µM, the ULOQ value will be imputed for analysis purposes.

If the measured antigenic AAT levels are below the LLOQ of 2.63 µM, the LLOQ value will be imputed for analysis purposes; if the measured antigenic AAT levels are above the ULOQ of 45 µM, the ULOQ value will be imputed for analysis purposes.

If the measured blood Z-polymer levels are below the LLOQ of 0.469 mg/L, the LLOQ value will be imputed for analysis purposes; if the measured blood Z-polymer levels are above the ULOQ of 2000 mg/L, the ULOQ value will be imputed for analysis purposes.

If the measured liver Z-polymer levels are below the LLOQ, the LLOQ value will be imputed for analysis purposes; if the measured liver Z-polymer levels are above the ULOQ of, the ULOQ value will be imputed for analysis purposes.

	Percent Stain Area: (unit = %)	H-Score: (unit = none)	Globule Density: (unit = number of globules/mm^2)
LLOQ	0.000%	0	0
ULOQ	100.000%	300	1000000

According to CSP (V2.0), "*There will be no further screening or enrollment, and no further study drug dosing, based on Sponsor decision to stop dosing in this study as of 25 September 2023*.". No subjects have had any post-treatment liver biopsy. The secondary endpoints related to liver Z-polymer will not be analyzed.

The observed values and change from baseline of the other secondary endpoints (functional AAT, antigenic AAT, and blood Z-polymer) will be summarized descriptively by group and overall at each visit.

9.3.3 Multiplicity Adjustment

There will be no multiplicity adjustment performed in the analysis of this study.

9.4 Safety Analysis

Safety is one of the secondary objectives of this study. All safety analyses will be performed based on the Safety Set by group and overall.

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

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

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. AEs will be classified as pretreatment, treatment-emergent, or post-treatment as follows:

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

Treatment-emergent AEs: AEs that worsened (either in severity or seriousness) or started on or after the first dose date of study drug through the end of the TE Period

Post-treatment AE: AE that worsened or that was newly developed 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.

The number and percentage of subjects experiencing TEAEs will be summarized by the MedDRA SOC and PT. AE summary tables will be presented only for TEAEs by group and overall 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 at different course of the study treatment (pre-treatment, under-treatment, and post-treatment) 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. The observed values and change from baseline values of the continuous hematology, chemistry, and coagulation results will be summarized by groups 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 group. The threshold analysis criterion shift from baseline will also be summarized descriptively. The threshold analysis criteria are provided in Appendix D.

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 listed 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 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 corrected by Fridericia's formula (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 group. The threshold analysis criteria are provided in Appendix D.

In addition, the number and percentage of subjects by maximum treatment-emergent value of QT/QTcF intervals, categorized as ≤450 msec, >450 msec and ≤480 msec, >480 msec and ≤500 msec, and >500 msec, as well as maximum treatment-emergent increase from baseline value of QT/QTcF intervals, categorized as >30 and ≤60 msec, and >60 msec and maximum treatment-emergent decrease from baseline value of QT/QTcF intervals, categorized as ≥ 30 msec, will be provided based on scheduled and unscheduled 12 lead ECG measurements.

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 group at each visit and time point. 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 group. The threshold analysis criteria are provided in Appendix D.

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 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

Interim analyses (IA) may be performed at any time at the discretion of the sponsor for internal decision-making.

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

10.2 Independent Data Monitoring Committee Analysis

Not applicable.

11 REFERENCES

Not applicable.

12 APPENDICES

Appendix A: Analysis Visit Windows for Efficacy, Safety, [redacted] Assessments

Table 12-1 Analysis Visit Windows for Efficacy, Safety, [redacted] Assessments

Assessment	Analysis Visit[1, 2]	Target Study Day	Analysis Visit Window (in study days)[3, 4, 5, 6]
Efficacy Assessments			
• Functional AAT Level • Antigenic AAT Level • Z-polymer	Day 1 (Baseline)	1	≤ 1 Pre-dose
	Day 7	7	[1 Post-dose, 11]
	Day 15	15	(11, 17]
	Day 21	21	(17, 23]
	Day 28	28	(23, 32]
	Wk 6	42	(32, 49]
	Wk 8	56	(49, 63]
	Wk 12	84	(63, 91]
	Wk 16	112	(91, 119]
	Wk 20	140	(119, 147]
	Wk 24	168	(147, 196]
	Wk 32	224	(196, 252]
	Wk 40	280	(252, 308]
	Wk 48	336	(308, Last Dose Day+1]
	Day 14 Safety Follow-up	Not applicable	Use nominal visit
	Day 28 Safety Follow-up	Not applicable	Use nominal visit
Safety Assessments			
• Serum Chemistry • Hematology • Coagulation • Vital signs • Pulse oximetry	Day 1 (Baseline)	1	≤ 1 Pre-dose
	Day 7	7	[1 Post-dose, 11]
	Day 15	15	(11, 17]
	Day 21	21	(17, 23]
	Day 28	28	(23, 32]
	Wk 6	42	(32, 49]
	Wk 8	56	(49, 63]
	Wk 12	84	(63, 91]
	Wk 16	112	(91, 119]
	Wk 20	140	(119, 147]
	Wk 24	168	(147, 196]
	Wk 32	224	(196, 252]
	Wk 40	280	(252, 308]
	Wk 48	336	(308, Last Dose Day+2]
	Day 14 Safety Follow-up	Not applicable	Use nominal visit
	Day 28 Safety Follow-up	Not applicable	Use nominal visit

Table 12-1 Analysis Visit Windows for Efficacy, Safety, [redacted] Assessments

• Standard 12-lead ECG	Day 1 (Baseline) Day 1 3 Hours Post-dose Day 7 Pre-dose Day 7 3 Hours Post-dose Day 28 Wk 12 Wk 24 Wk 48 Day 14 Safety Follow-up Day 28 Safety Follow-up	1 Not applicable Not applicable Not applicable 28 84 168 336 Not applicable Not applicable	≤ 1 Pre-dose Use nominal visit Use nominal visit Use nominal visit (7, 36] (36, 126] (126, 252] (252, Last Dose Day+2] Use nominal visit Use nominal visit
• Weight	Day 1 (Baseline) Wk 24 Wk 48 Day 14 Safety Follow-up Day 28 Safety Follow-up	1 168 336 Not applicable Not applicable	≤ 1 Pre-dose (1, 252] (252, Last Dose Day+2] Use nominal visit Use nominal visit

Notes:

1. Visit name for analysis purpose is used to report data in tables and figures.
2. For ETT Visit, the following rules will be used:
   - If ETT Visit replaces Day 28 Safety Follow-up Visit when it occurs ≥ 3 weeks after the last dose of study drug, it will be mapped as Analysis Visit Day 28 Safety Follow-up.
3. For efficacy assessments, the analysis visit window for Day 1, Day 7, Day 15, Day 21, Day 28, Wk 6, Wk 8, Wk 12, Wk 16, Wk 20, Wk 24, Wk 32, Wk 40 and Wk 48 will only be implemented for the assessments conducted on or before 1 day after the last dose of study drug. For safety assessments, the analysis visit window Day 1, Day 7, Day 15, Day 21, Day 28, Wk 6, Wk 8, Wk 12, Wk 16, Wk 20, Wk 24, Wk 32, Wk 40 and Wk 48 will only be implemented for the assessments conducted on or before 2 days after the day of last dose of study drug.
4. The analysis visit windows will be applied using the following rules for both scheduled and unscheduled visits:
   - If no measurement is available within a visit window, the measurement will be considered missing for the visit.
   - If there is more than 1 numerical measurement available within a visit window, use the following rules:
     - The measurement closest to the target day will be used.
     - If there are multiple measurements with the same distance from the target day, the latest measurement will be used.
     - Except for ECGs, if two measurements (one scheduled and one unscheduled) occur on the same day, the scheduled assessment will be used.

- For ECGs, if multiple ECG triplicates are obtained on the same day during the TE period, the mean of the ECGs on that day will be used as the ECG value on that day for summary purpose.

5. For measurements collected on the date of first dose of study drug, if it cannot be determined whether the measurement is before or after the first dose:
   - If a scheduled measurement is pre-dose in CSP, it will be treated as a pre-dose observation. If a scheduled measurement is post-dose in CSP, it will be treated as a post-dose observation.
   - Unscheduled measurements will be treated as post-dose observations.
6. The analysis visit windows will be implemented in the following order:
   - Step 1: The analysis visit window "Use nominal visit" is implemented. The nominal visits used in this step will be excluded in the next step.
   - Step 2: The other analysis visit windows are implemented.

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

Missing or partial dates will be imputed for medication. Algorithm for 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.

Algorithm for 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.

Missing data algorithms will be reviewed to ensure the algorithms work. For example, end date will not be before the start date after the imputation.

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

Table 12-2 Prior and Concomitant 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

C: Concomitant; P: Prior; A: Post

Imputation rules for missing and/or partial dates of non-pharmacological treatment/procedure will follow the same imputation rule.

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 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 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 TE period to determine whether the AE is 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 AE end date is missing, then impute the AE start Month and Day as the Month and Day of 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 TE period to determine whether the AE is pretreatment AE or TEAE.
- **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 with no imputation. Also 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 TEAE.

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

Appendix D: Criteria for Threshold Analysis

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

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

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

Parameter	Threshold Analysis	Comments
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2xULN	FDA DILI Guidance Jul 2009.
GGT	>ULN - ≤2.5xULN >2.5 - ≤5.0xULN >5.0 - ≤20.0xULN >20.0xULN	CTCAE grade 1-4
Clinical Chemistry (NON-LFT)		
Albumin	<LLN - ≥30 g/L <30 - ≥20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>1x - ≤1.5xULN >1.5x - ≤2xULN >2x - ≤5xULN >5xULN	Criteria based upon CTCAE
Creatinine	>ULN - ≤1.5xULN >1.5 - ≤3.0xULN >3.0 - ≤6.0xULN >6.0xULN	CTCAE grades 1-4
Lipase	>ULN - ≤1.5xULN >1.5x - ≤2xULN >2x - ≤5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
Creatine kinase	>ULN - ≤2.5xULN >2.5 - ≤5xULN >5 - ≤10xULN >10xULN	CTCAE grades 1-4
Hematology		
Hemoglobin	Hgb decreased (anemia) <LLN - ≥100 g/L <100 - ≥80 g/L <80 g/L	CTCAE grade 1-3
	Hgb increased >ULN - ≤20 g/L above ULN >20 g/L above ULN - ≤40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3
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

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

Parameter	Threshold Analysis	Comments
	Platelet increased >ULN	No CTCAE available
Reticulocytes/Erythrocytes (%)	<LLN >ULN	No CTCAE
Coagulation		
Activated partial thromboplastin time (PTT)	>ULN - ≤1.5xULN >1.5 - ≤2.5xULN >2.5xULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤1.5xULN >1.5 - ≤2.5xULN >2.5 x ULN	CTCAE grade 1-3

Table 12-4 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
HR	Bradycardia <50 bpm <45 bpm Decrease from baseline ≥10 bpm Decrease from baseline ≥20 bpm <50 bpm and decrease from baseline ≥10 bpm <50 bpm and decrease from baseline ≥20 bpm	Per HV grade 2, 3, plus shift change
	Tachycardia >100 bpm >115 bpm >130 bpm Increase from baseline ≥10 bpm Increase from baseline ≥20 bpm >100 bpm and increase from baseline ≥10 bpm >100 bpm and increase from baseline ≥20 bpm	Per HV grade 1, 2, 3, plus shift change
PR	≥240 ms ≥300 ms ≥200 ms and increase from baseline ≥40 ms ≥200 ms and increase from baseline ≥100 ms	
QRS	>110 ms >160 ms Increase from baseline ≥20 ms Increase from baseline ≥40 ms	

Table 12-4 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
QTc	>450 to <500ms (Male) or >470 to <500ms (Female) ≥500 ms Increase from baseline Increase from baseline >10 ms Increase from baseline >20 ms Increase from baseline >40 ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula.

Table 12-5 Threshold Analysis Criteria for Vital Signs

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

Table 12-5 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
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	

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

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/lr/show-details/?idP=138978 [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/lr/show-details/?idP=138979 [Accessed 16 August 2018].

Sanja Stanojevic. GLI-2012 - SAS Macro (Version 2, 7 April 2013). Global Lung Function Initiative. [online] Available at: https://www.ers-education.org/lr/show-details/?idP=138988 [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 FEV$_1$ measurement to calculate ppFEV$_1$; for spirometry performed on or after informed consent, use height at screening for 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 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.