VERTEX

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Interim Analysis #1): (Methods)

Protocol Number VX15-661-113, Version 1.2

A Phase 3, Open-label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661 in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous or Heterozygous for the *F508del-CFTR* Mutation

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Version: 1.0

Version Date of SAP: 11 January 2017

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3 INTRODUCTION

This SAP is for the interim analysis (IA) following completion of the Part A of the study and is based on the following:

- approved clinical study protocol (CSP) (Version 1.2, dated 26 May 2016),
- approved electronic case report form (eCRF) (Version 2.0, dated 11 Oct 2016).

The protocol states that a review of the safety, tolerability, and pharmacokinetic (PK) data will be completed by an internal Vertex team after Part A. The objective of this IA is the same as the objective for Part A, as listed in Section 4.

Study VX15-661-113 is a Phase 3, 2-part (Part A and Part B), open-label, multicenter study evaluating the PK, safety, and tolerability of multiple doses of tezacaftor (TEZ; VX-661) in combination with ivacaftor (IVA; VX-770) in subjects 6 through 11 years of age with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation.

This SAP (Methods) documents the safety objective of Part A and describes the planned statistical analyses and data presentations for the same. Analysis addressing the clinical pharmacology objective (i.e., the primary objective of Part A) is described in the interim version of the Clinical Pharmacology Data Analysis Plan (CPAP), which will be developed separately.

The Vertex Biometrics Department will perform the analysis of Part A safety data as defined in this plan; SAS (Version 9.2 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the data cut for the IA and if the methods in this SAP differ from the methods described in the protocol, the SAP prevails.

4 STUDY OBJECTIVES FOR PART A

4.1 Primary Objective

To evaluate the PK of TEZ and IVA after administration of multiple doses of TEZ in combination with IVA

4.2 Secondary Objectives

- To evaluate the PK of TEZ metabolites, M1-TEZ and M2-TEZ, and IVA metabolites, M1-IVA and M6-IVA, after administration of multiple doses of TEZ in combination with IVA
- To evaluate the safety and tolerability of multiple doses of TEZ in combination with IVA

5 STUDY ENDPOINTS FOR PART A

5.1 Primary Endpoints

TEZ and IVA PK parameters, including maximum observed concentration (C_{max}), area under the concentration versus time curve during a dosing interval (AUC_{τ}), and other PK parameters as appropriate

5.2 Secondary Endpoints

- M1-TEZ, M2-TEZ, M1-IVA, and M6-IVA PK parameters, including Cmax, AUCτ, and other PK parameters as appropriate
- Safety and tolerability of TEZ in combination with IVA as determined by adverse events (AEs), clinical laboratory values (serum chemistry, hematology, coagulation studies, lipids, vitamins, and urinalysis), standard 12-lead electrocardiograms (ECGs), vital signs, pulse oximetry, and spirometry

6 STUDY DESIGN

6.1 Overview of Study Design

This is a Phase 3, 2-part (Part A and Part B), open-label, multicenter study evaluating the PK, safety, and tolerability of multiple doses of TEZ in combination with IVA in subjects 6 through 11 years of age with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation. Efficacy will also be evaluated in Part B. Part A is composed of 2 weight-based cohorts, which will be enrolled simultaneously, and Part B is composed of a single cohort. Subjects who participate in Part A may participate in Part B.

Part A

Approximately 16 subjects total, approximately 8 subjects in each cohort (Cohort 1 [subjects weighing <25 kg at baseline] and Cohort 2 [subjects weighing ≥25 kg at baseline]), are planned for enrollment.

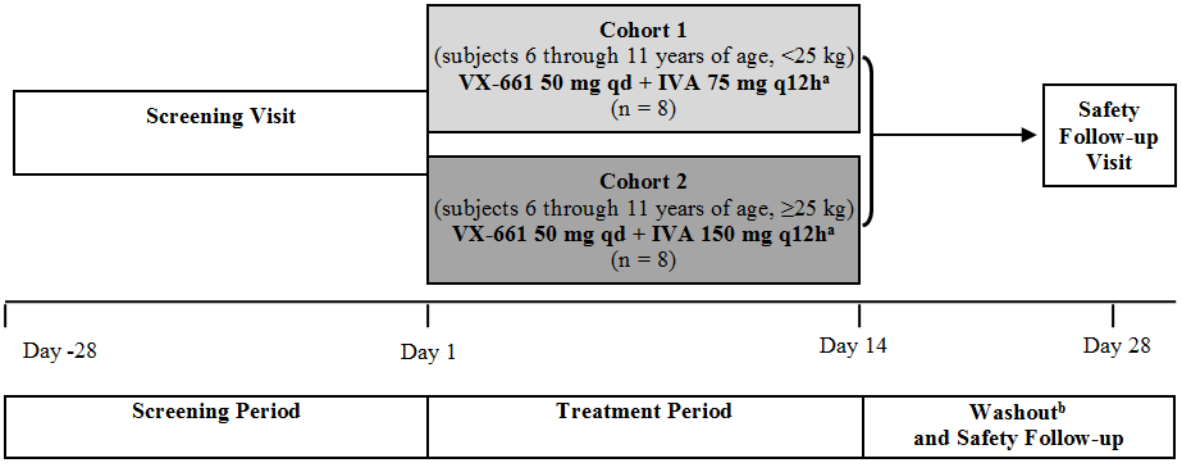
Part A includes the following:

- Screening Period (Day -28 through Day -1)
- Treatment Period (Day 1 through Day 14)
- Washout Period (Day 14 to Day 28 [± 3 days])
- Safety Follow-up Visit (14 [± 3] days after the last dose of study drug)

Figure 6-1 depicts the schematic for the Part A study design. After obtaining written informed consent (and assent, if applicable), Screening Visit assessments will be completed at any time during the period of 4 weeks (Day -28 through Day -1) before the first dose of the study drug (Day 1). During the Treatment Period, subjects will be administered TEZ 50 mg daily (qd) in combination with IVA, either 75 mg (subjects <25 kg at baseline) or 150 mg (subjects ≥25 kg at baseline), every 12 hours (q12h) for 14 days. A 2-week Washout Period (Day 14 to Day 28 [± 3 days]) will be included in order to evaluate the off-drug response. A Safety Follow-up Visit (SFUV) is scheduled to occur 14 (± 3) days after the last dose of study drug for all subjects, including subjects who permanently discontinue from study treatment for any reason.

A review of safety, tolerability, and PK data will be completed by an internal Vertex team after Part A to select the TEZ dose for Part B.

Figure 6-1 Schematic of Study Design for Part A



IVA: ivacaftor; n: number of subjects; q12h: every 12 hours; qd: daily.
Note: Approximately 16 subjects (approximately 8 subjects in each cohort) are planned for enrollment.
[a] Weight refers to weight at baseline. Study drug will be administered from Day 1 through Day 14. On Day 14, only the morning dose of study drug will be administered.
[b] A 2-week Washout Period (Day 14 to Day 28 ± 3 days) will be included in order to evaluate the off-drug response.

Part B

Approximately 56 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 50 subjects are expected to complete Part B.

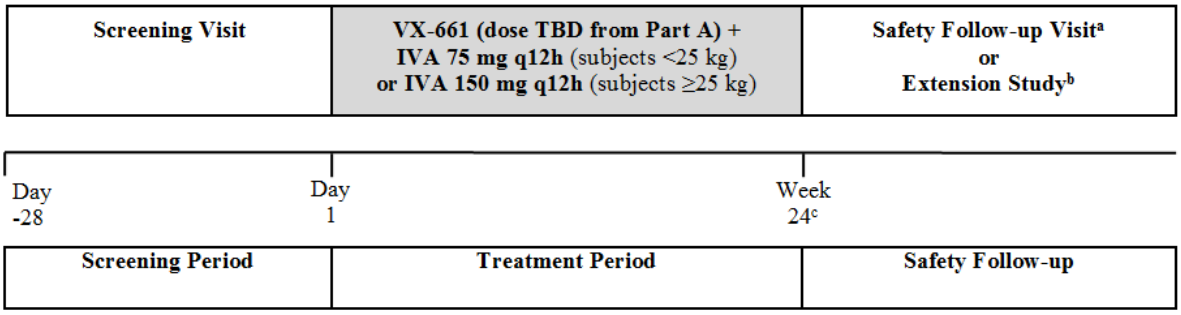
Part B includes the following:

- Screening Period (Day -28 through Day -1)
- Treatment Period (Day 1 through Week 24 [± 5 days])
- SFUV (4 weeks [± 7 days] after the last dose of study drug)

Figure 6-2 depicts the schematic for the Part B study design. After obtaining written informed consent (and assent, if applicable), Screening Visit assessments will be completed at any time during the period of 4 weeks (Day -28 through Day -1) before the first dose of study drug (Day 1). During the Treatment Period, subjects will be administered TEZ (dose to be determined in Part A) in combination with ivacaftor, either 75 mg (subjects <25 kg at baseline) or 150 mg (subjects ≥25 kg at baseline), q12h for 24 weeks. At the Week 24 Visit, subjects who complete study drug treatment will be offered the opportunity to enroll in an extension study evaluating TEZ in combination with IVA (enrollment will be based on the eligibility criteria specified within the extension study). Subjects who prematurely discontinue study drug treatment are not eligible to rollover into the extension study.

A SFUV is scheduled to occur 4 weeks (± 7 days) after the last dose of study drug. The SFUV is not required for subjects who have enrolled in the extension study within 28 days after the last dose of study drug. Subjects who permanently discontinue study drug treatment will have an Early Treatment Termination (ETT) Visit and a SFUV.

Figure 6-2 Schematic of Study Design for Part B



IVA: ivacaftor; q12h: every 12 hours; qd: daily; TBD: to be determined.
Note: Weight refers to weight at baseline.

[a] The Safety Follow-up Visit will occur 4 weeks [± 7 days] after last dose and is not required for subjects who have enrolled in the extension study within 28 days after the last dose of study drug.

[b] At the Week 24 Visit, subjects who complete study drug treatment will be offered the opportunity to enroll in an extension study evaluating VX-661 in combination with ivacaftor. Subjects who prematurely discontinue study drug treatment are not eligible to rollover into the extension study.

[c] The last dose of study drug will be the evening dose administered the day before the Week 24 Visit.

6.2 Sample Size and Power for Part A

Sample size calculations were conducted to estimate the precision in determining TEZ clearance in pediatric subjects in the 2 weight-based cohorts. The method used noncompartmental analysis-based PK parameters, such as clearance and volume, in adults with the assumption that there is similar variability in clearance in adults and pediatric subjects 6 through 11 years of age within each weight group. The calculations indicate that data from 8 subjects will allow 80% power to target a 95% CI within 60% and 140% of the geometric mean estimate of clearance for TEZ in each pediatric subgroup (cohort). Therefore, approximately 16 subjects (approximately 8 subjects in each cohort) are planned for enrollment in Part A.

6.3 Randomization for Part A

Not applicable because subjects will receive treatment based on weight at baseline.

6.4 Blinding and Unblinding for Part A

Not applicable because this is an open-label study.

7 ANALYSIS SETS FOR PART A

The following analysis sets are defined: Part A - All Subjects Set and Part A - Safety Set. Assignment of subjects to analysis sets will be done prior to the data-cut for the IA following completion of Part A.

The **Part A - All Subjects Set** is defined as subjects who consented to Part A of the study or received at least 1 dose of study drug in Part A of the study.

The **Part A - Safety Set** is defined as all subjects who received at least 1 dose of study drug in Part A of the study.

8 STATISTICAL ANALYSIS FOR PART A

8.1 General Considerations

The IA will be restricted to data only from Part A (includes the off-treatment period between the Day 14 Visit and SFUV).

All individual subject data for those who consented to Part A or were dosed in Part A will be presented in data listings. The Schedule of Assessments is provided in Section 10.1. The precision standards are provided in Section 10.3.

Continuous variables will be summarized by treatment (TEZ 50 mg qd + IVA 75 mg q12h, TEZ 50 mg qd + IVA 150 mg q12h) and overall using the following descriptive summary statistics: number of subjects (n), mean, standard deviation (SD), median, minimum value (min), and maximum value (max).

Categorical variables will be summarized by treatment (TEZ 50 mg qd + IVA 75 mg q12h, TEZ 50 mg qd + IVA 150 mg q12h) and overall using counts and percentages.

Treatment-emergent (TE) period will correspond to data from the first dose of study drug in Part A to the SFUV in Part A or 14 days after the last dose in Part A for subjects who do not have a SFUV.

Baseline for Part A is defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in Part A. For ECGs, baseline will be the average of the 3 pretreatment measurements on Day 1 of Part A.

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

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

Unscheduled Visits: Subject data obtained during unscheduled visits will not be summarized but will be included in subject data listings only, except for the analysis of the maximum value during TE period and maximum changes from baseline during TE period (see Section 8.3.3). Unscheduled visit values will not be used to impute missing scheduled visit values, except for the baseline calculation.

Visit Windowing Rules: Due to the short duration of the Treatment Period, visit windowing will not add significant value to the analysis and therefore will not be applied.

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

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

8.2 Background Characteristics for Part A

8.2.1 Subject Disposition

The number of subjects in the following categories will be presented by treatment group:

- Part A - All Subjects Set
- Part A - Safety Set

In the same table, the number and percentage (based on Part A - Safety Set) of subjects in each of the following disposition categories will be presented by treatment group:

- Completed study drug treatment
- Prematurely discontinued the treatment (TEZ or IVA) and the reasons for discontinuations
- Completed study
- Prematurely discontinued study and the reasons for discontinuations

A listing will be provided for subjects who discontinued treatment or who discontinued study with reasons for discontinuations.

8.2.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics data will be summarized by treatment group based on the Part A - Safety Set.

Demographic data will include the following:

- Age at screening
- 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, and Other)

Baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- FEV_1
- $ppFEV_1$

8.2.3 Medical History

Medical history in this study will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA).

For the Part A - Safety Set, medical history will be summarized descriptively by treatment group, system organ class (SOC) and preferred term (PT). The corresponding data listing will also be provided.

In addition, a listing of subjects reported to have had positive cultures for respiratory pathogens in 2 years prior to screening (i.e., answered yes on the respiratory microbiology form) will be presented. A listing of ophthalmology history will also be presented.

8.2.4 Prior and Concomitant Medications

Medications used in this study will be coded by using the World Health Organization Drug Dictionary Enhanced (WHO-DDE) and categorized as follows:

- **Prior medication**: any medication that started before the first dose of study drug in Part A, regardless of when it ended.

- **Concomitant medication**: medication continued or newly received during the TE period for Part A.
- **Post-treatment medication**: medication continued or newly received after the TE period for Part A. For those subjects from Part A who enrolled in Part B, medications that continued or were newly received on or after the first dose of study drug in Part B will not be considered as post-treatment medication.

A given medication can 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 a missing or partially missing start/end date or time and it cannot be determined whether the medication was taken before initial dosing, concomitantly, or post-treatment, it will be considered as prior, concomitant, and post-treatment.

For the Part A - Safety Set, concomitant medications will be summarized descriptively by 1) treatment group, preferred name (PN); and 2) treatment group, anatomic class (ATC) level 1, ATC level 2, and PN. Prior medications and post-treatment medications will be listed for each subject.

As an intermediate step for programming purposes, medications with missing or partially missing start dates will use 2000 to impute for the missing year, January for the missing month, and 1 for the missing day. Medications with missing or partially missing stop dates will use 2050 to impute for the missing year, December for the missing month, and the last day of the month for the missing day.

8.2.5 Study Drug Exposure

Exposure summaries will be based on the Part A - Safety Set and presented by treatment group.

Duration of study drug exposure is defined as follows: last dose date in Part A – first dose date in Part A + 1 day, regardless of any interruption in dosing between the first and the last dose.

Duration of study drug exposure will be summarized descriptively (number, mean, SD, median, minimum, and maximum).

8.2.6 Important Protocol Deviations

An important protocol deviation (IPD) is any PD 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. The rules for identifying IPDs will be finalized prior to the data-cut for the IA following completion of Part A. The rules will be developed by a team consisting of, at a minimum, the Medical Monitor, the Study Biostatistician, the Clinical Data Manager, and the Clinical Operations Study Lead. This team will review the list of protocol deviations, to develop rules for identifying IPDs.

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

- Violation of subjects rights, safety or well-being
- Subject entered the study despite violation of an inclusion or exclusion criteria
- Subject received the wrong treatment or incorrect doses

Occurrence of any of these events should be considered as potential IPDs, but the team should categorize them as IPDs only if they have the potential to significantly affect interpretation of study results or significantly affects the subject's rights, safety or well-being. The team should construct rules for identifying IPDs rather than identifying individual subjects with IPDs.

IPDs (from the site deviation log) will be provided as a subject data listing.

8.3 Safety Analysis for Part A

Safety is a secondary objective of this study, and the safety endpoints included for analyses are as follows:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory measurements (chemistry, hematology, coagulation, lipids, vitamins, and urinalysis)
- Standard 12-lead ECG
- Vital signs
- Pulse oximetry
- Spirometry

Safety analyses will be performed by treatment group. Safety analysis will be conducted for the Part A - Safety Set and subjects analyzed according to the treatment they received. Only descriptive analysis of safety will be performed (i.e., no statistical hypothesis testing will be performed).

Table 8-1 shows the safety summaries (e.g., raw value, change from baseline, incidence, and clinical abnormalities) that will be summarized for TEAEs, clinical laboratory values, 12-lead ECG, vital signs, pulse oximetry, spirometry and physical examination.

The incidence of TEAEs will be summarized. For the non-AE safety evaluations (clinical laboratory, ECGs, vital signs, pulse oximetry and spirometry), raw values, and changes from baseline will be summarized as indicated in Table 8-1. For example, an "X" under the raw value column (second column) means that the raw values for the safety evaluation will be summarized; an "X" under the Change column (third column) means that change will be summarized.

Throughout this section, "change" refers to absolute change from baseline.

Table 8-1 Summaries Planned for Safety Data

Safety Assessment	Incidence	Raw Value	Change	Clinical Abnormalities
TEAEs	X			Present in listing only
Chemistry/Hematology/ Coagulation/Vitamins/ Lipids		X	X	Present in listing only
Urinalysis		Present in listing only		Present in listing only
12-lead ECG		X	X	Present in listing only
Vital signs		X	X	Not applicable
Pulse oximetry		X	X	Not applicable
Spirometry		X	X	Not applicable
Physical Examination		Present in listing only		Not applicable

TEAE: Treatment-emergent adverse event; ECG: electrocardiogram; X: safety assessment will be summarized in tables.

8.3.1 Adverse Events

AEs will be coded according to MedDRA and categorized as pretreatment AEs, TEAEs, or post-treatment AEs:

- **Pretreatment AE:** any AE that started before the first dose of study drug in Part A.
- **TEAE:** any AE that increased in severity or that was newly developed during the TE period for Part A.
- **Post-treatment AE:** any AE that increased in severity or that was newly developed beyond the TE period for Part A. For subjects from Part A who enrolled in Part B, an AE that increased in severity on or after the first dose of study drug in Part B will not be considered as a post-treatment AE.

For AEs with missing or partial start dates, if there is no clear evidence that the AEs started before or after study treatment for Part A, then the AEs will be classified as TEAEs. As an intermediate step for programming purposes, imputation rules for missing or partially missing AE start/end dates are defined in Section 10.4.

AE summary tables will be presented for TEAEs only and will include the following:

(1) all TEAEs

(2) related (defined as possibly related, related, or missing) TEAEs

(3) serious TEAEs

(4) Grade 3/4 TEAEs

(5) TEAEs leading to treatment discontinuation

Summaries will be presented by MedDRA SOC and PT using frequency counts and percentages by treatment group. A subject with multiple occurrences of the same TEAE or a continuing TEAE will be counted only once.

An overview of all TEAEs will be summarized in the following categories:

- Any TEAEs
- TEAEs by relationship
- Related TEAEs
- TEAEs by severity
- Grade 3/4 TEAEs
- Serious TEAEs
- Related Serious TEAEs
- TEAEs leading to treatment discontinuation (this will include TEAEs leading to discontinuation of either TEZ tablet or the IVA tablet)
- TEAEs leading to treatment interruption (this will include TEAEs leading to interruption of either TEZ tablet or the IVA tablet)
- TEAEs leading to death

In addition, a listing containing individual subject adverse event data for TEAEs leading to treatment discontinuation, treatment interruptions, SAEs and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.

For all AEs, the action taken on the CRF for TEZ is collected separately from the AE action taken for IVA. As a result, it is possible that in the AE dataset, the AE actions taken for the two agents are different. The summary of “TEAE Leading to Treatment Discontinuation” and listings of "TEAE Leading to Treatment Discontinuation", "TEAE Leading to Treatment Interruption" account for discontinuation and interruptions for either agent.

8.3.2 Clinical Laboratory

For treatment-emergent laboratory measurements, the raw values and change from baseline values of the continuous hematology, chemistry, vitamin, lipids and coagulation results will be summarized in SI units by treatment group at each scheduled time point.

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

In addition, a listing containing individual subject hematology, chemistry, vitamin, lipids and coagulation results outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled visits.

8.3.3 Standard 12-Lead Electrocardiogram

For treatment-emergent ECG measurements, a summary of raw values and change from baseline values will be provided by treatment group at each scheduled time point for the following standard 12-lead ECG measurements: PR, QTc for HR intervals (QTcF), QRS duration, and HR.

In addition, the number and percentage of subjects by maximum value of QT/QTcF intervals during TE period, categorized as ≤450 msec, >450 msec and ≤480 msec, >480 msec and ≤500 msec, and >500 msec, as well as maximum change from baseline value of QT/QTcF intervals during TE period, categorized as ≤0 msec, >0 and ≤30 msec, >30 msec and ≤60 msec, and >60 msec, will be provided.

8.3.4 Vital Signs

For treatment-emergent vital signs measurements, the raw values and change from baseline values will be summarized by treatment group at each scheduled time point for the following: systolic and diastolic blood pressure (mm Hg), body temperature (^{o}C), HR (beats per minute), and respiratory rate (breaths per minute).

8.3.5 Pulse Oximetry

For treatment-emergent percent of oxygen saturation by pulse oximetry, a summary of raw values and change from baseline values will be provided by treatment group at each scheduled time point.

8.3.6 Spirometry

For spirometry measurements, a summary of raw values, absolute and relative change from baseline values will be provided by treatment group at each scheduled time point for the following parameters: FEV_1 (L), forced vital capacity (FVC) (L), FEV_1/FVC (ratio), forced expiratory flow ($FEF_{25\%-75\%}$) (L/s), $ppFEV_1$, percent predicted FVC, percent predicted FEF, and percent predicted FEV_1/FVC. The predicted values for spirometry will be calculated using the Global Lung Initiative (GLI) equation[1]. See section 10.2 for details on GLI equation.

8.3.7 Physical Examination

Physical examination findings will be presented as a data listing only.

8.3.8 Other Safety Analyses

Not Applicable.

9 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.

10 APPENDICES

10.1 Schedule of Assessments

Table 10-1 Study VX15-661-113: Part A Screening

Assessment	Screening Visit (Day -28 to Day -1)
Informed consent (and assent, if applicable)	X
Demographics	X
Medical history	X
Ophthalmological history[a]	X
Weight, height, and vital signs[b,c]	X
Pulse oximetry[c]	X
Ophthalmologic examination[a,d]	X
Full physical examination[e]	X
Standard 12-lead ECG[f]	X
Spirometry[g]	X
Sweat chloride[h]	X
CFTR genotype[i,j]	X
Serum pregnancy test (female subjects of childbearing potential)[i,k]	X
Serum chemistry[i]	X
Vitamin levels[i]	X
Hematology and coagulation studies[i]	X
Urinalysis[i]	X
Inclusion/exclusion criteria review	X
Prior and concomitant medications	Continuous from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit
AEs and SAEs	Continuous from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit

[a] Refer to Section 11.7.6 of CSP for details.
[b] Weight and height will be measured with shoes off. BMI will be derived from assessment of height and weight.
[c] Vital signs and pulse oximetry will be collected after the subject has been seated or supine for at least 5 minutes (see Section 11.7.4 of CSP).
[d] An ophthalmologic examination will be conducted by a licensed ophthalmologist. The examination does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the start of the Screening Period. Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination. Subjects with clinically significant cataracts, lens opacity, Y suture, or lamellar rings will be excluded (refer to Section 9.2 of CSP).
[e] Refer to Section 11.7.4 of CSP for details.
[f] A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes (refer to Section 11.7.5 of CSP). The ECG will be performed before any other procedures that may affect heart rate.
[g] Spirometry may be performed pre- or post-bronchodilator (refer to Section 11.6.1 of CSP).
[h] A sweat chloride test must be performed if an eligible sweat chloride value is not available in the subject's medical records (refer to Section 11.6.2 of CSP). For subjects using a sweat chloride value documented in their medical record to establish eligibility, the sweat chloride test at the Screening Visit is optional.
[i] Refer to Section 11.7.2 of CSP for details.
[j] All subjects will be tested to assess *CFTR* genotype, regardless of availability of a previous *CFTR* genotype lab report. In subjects with confirmed *R117H* mutation, linkage to poly-T track polymorphisms will also be determined from a second specimen. Specific instructions will be provided in the Laboratory Manual.
[k] Any female subject who does not meet the criteria for non-childbearing potential (refer to Section 11.7.8.1 of CSP) is considered to be of childbearing potential and must have a serum pregnancy test.

Table 10-1 Study VX15-661-113: Part A Screening

Assessment	Screening Visit (Day -28 to Day -1)

AE: adverse event; BMI: body mass index; CF: cystic fibrosis; *CFTR*: *CF transmembrane conductance regulator* gene; ECG: electrocardiogram; ICF: informed consent form; SAE: serious adverse event

Table 10-2 Study VX15-661-113: Part A Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Day 1	Day 2	Day 4 (± 1 day)	Day 7 (± 1 day)	Day 14	Day 21 (± 1 day)	Day 28 Safety Follow-up Visit (14 [± 3] days after the last dose)
Clinic visit	X	X		X	X	X	X
Telephone contact[b]			X				
Safety Assessments							
Weight and height[c]	X				X		X
Vital signs[d]	X	X		X	X		X
Pulse oximetry[d]	X	X		X	X		X
Full physical examination[e]	X				X		X
Standard 12-lead ECG[f]	X[g]	X		X	X[g]		X
Spirometry[h]	X	X		X	X		X
Pregnancy test (female subjects of childbearing potential)[i,j]	X (urine)						X (serum)
Serum chemistry[j]	X			X	X		X
Lipid panel[j,k]	X				X		
Vitamin levels[j]					X		
Hematology[j]	X			X	X		X
Coagulation studies[j]						X	

[a] All assessments will be performed before study drug dosing unless noted otherwise (refer to Section 11.1 of CSP). When repeats of an assessment are required postdose at a given visit, the assessment will be collected only once if study drug is not administered on the day of the visit (i.e., study drug interruption or permanent discontinuation of study drug).

[b] Telephone contact will be made to assess the subject's status, any AEs, concomitant medications, treatments, and procedures.

[c] Weight and height will be measured with shoes off. BMI will be derived from assessment of height and weight.

[d] Vital signs and pulse oximetry will be collected after the subject has been seated or supine for at least 5 minutes (refer to Section 11.7.4 of CSP).

[e] At other visits, symptom-directed physical examinations will occur if triggered by AEs or if deemed necessary by the investigator (refer to Section 11.7.4 of CSP).

[f] Standard 12-lead ECGs will be performed before study drug dosing (unless noted otherwise) after the subject has been supine for at least 5 minutes (refer to Section 11.7.5 of CSP).

[g] At the Day 1 and Day 14 Visits, standard 12-lead ECGs will be performed after the subject has been supine for at least 5 minutes at the following times: before the morning dose of study drug, and at 1.5, 3, 4, and 6 hours after the morning dose of study drug. ECGs collected on Day 1 before study drug dosing will be performed in triplicate. A window of ±15 minutes will be allowed around the nominal times for all postdose ECG assessments.

[h] Spirometry must be performed for all subjects before dosing and should be performed pre-bronchodilator (refer to Section 11.6.1 of CSP).

[i] Any female subject who does not meet the criteria for non-childbearing potential (refer to Section 11.7.8.1 of CSP) is considered to be of childbearing potential and must have a pregnancy test.

[j] Refer to Section 11.7.2 of CSP for details.

[k] Blood samples will be collected for the lipid panel following at least a 4-hour fast.

Table 10-2 Study VX15-661-113: Part A Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Day 1	Day 2	Day 4 (± 1 day)	Day 7 (± 1 day)	Day 14	Day 21 (± 1 day)	Day 28 Safety Follow-up Visit (14 [± 3] days after the last dose)
Urinalysis[j]	X				X		
Concomitant medications, treatments, and procedures	Continuous from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit						
AEs and SAEs	Continuous from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit						
PK Assessments							
PK Sampling	X[l]	X[l]			X[m]	X[m]	X[m]
Study Drug Administration							
VX-661 + IVA[n]	**VX-661 qd + IVA q12h Day 1 through Day 14 (morning dose only on Day 14)**						

AE: adverse event; BMI: body mass index; CF: cystic fibrosis; ECG: electrocardiogram; ICF: informed consent form; IVA: ivacaftor; PK: pharmacokinetic; q12h: every 12 hours; qd: daily; SAE: serious adverse event

---

[l] PK blood samples will be collected on Day 1 at 1, 2, 4, 5, and 24 hours (i.e., predose on Day 2) after the morning dose of study drug on Day 1. Acceptable windows for sampling times are shown in Table 11-1 of CSP.

[m] PK blood samples will be collected before the morning dose of study drug on Day 14 and at 1, 2, 4, and 5 hours after the morning dose of study drug on Day 14. A PK blood sample will also be collected at 168 hours (i.e., Day 21) after the morning dose of study drug on Day 14 and at the Safety Follow-up Visit. Acceptable windows for sampling times are shown in Table 11-1 of CSP.

[n] The study drug should be administered approximately 30 minutes after the start of consuming fat-containing food (e.g., standard "CF" high-fat, high-calorie meal or snack). Refer to Section 9.3 of CSP for details on study restrictions and Section 10.2 of CSP for details on study drug administration (e.g., fasting requirements). On days of scheduled visits, the dose of study drug will be administered at the clinical site after predose assessments have been completed. The last dose of study drug will be the morning dose on Day 14.

10.2 GLI Regression Equation and Implementation

Percent predicted values will be calculated for parameters of FEV_1, FVC, FEV1/FVC, and $FEF_{25\%-75\%}$ using the Quanjer GLI-2012 Regression Equations and Lookup Tables.

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

Quanjer GLI-2012 Regression Equations and Lookup Tables. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 7 April 2013. Available at: http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/quanjer-gli-2012-regression-equations-and-lookup-tables.aspx. Accessed 08 December 2015.

The instructions and tools on how to implement the Quanjer GLI-2012 equations are:

Implementing GLI-2012 regression equations. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 19 July 2015. Available at: http://www.ers-education.org/guidelines/global-lung-function-initiative/gli-2012-explained.aspx. Accessed 08 December 2015.

GLI-2012 - SAS Macro. Sanja Stanojevic. Version 2, 7 April 2013. Available at: http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/sas-macro.aspx. Accessed 08 December 2015.

10.3 Standards for Safety Variable Display in TFLs

Continuous Variables

The precision for continuous variables has been specified in the Vertex Standard Programming Rules document (Version 1.0, December 2015):

[redacted]

Categorical Variables: Percentages will be presented to 1 decimal place.

10.4 Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined below:

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, TEAE or post-treatment AE.

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, TEAE or post-treatment AE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site 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.

VERTEX

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan

Methods

Part B

Protocol Number VX15-661-113, Version 3.0

A Phase 3, Open-label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661 in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous or Heterozygous for the *F508del-CFTR* Mutation

Author of SAP: [redacted]

Version: 1.0

Version Date of SAP: 22 June 2018

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2 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
bpm	beats per minute
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
CRF	case report form
CRO	contract research organization
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDC	VX-661 100-mg/IVA 150-mg fixed-dose tablet
$FEF_{25-75\%}$	forced expiratory flow, midexpiratory phase
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
IVA	ivacaftor
LS means	Least squares means
LFT	liver function test
max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum value
MMRM	mixed model repeated measure
N	number of subjects
PD	pharmacodynamic/pharmacodynamics
PK	pharmacokinetic/pharmacokinetics
ppFEV1	percent predicted FEV1
PT	preferred term
q12h	every 12 hours
QRS	Q, R, and S-wave define the QRS-complex in an ECG
QT	QT interval: The duration of ventricular depolarization and subsequent repolarization; it is measured from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate with Fridericia's correction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SOC	system organ class

Abbreviation	Term
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHODD	World Health Organization Drug Dictionary Enhanced

4 INTRODUCTION

This statistical analysis plan (SAP) Methods, which describes the planned analyses for Study VX15-661-113 Part B, is based on the following:

- approved clinical study protocol (CSP) (Version 3.0, dated 19 July 2017),
- approved electronic case report form (eCRF) (Version 3.0, dated 25 Sep 2017).

Study VX15-661-113 is a Phase 3, 2-part (Part A and Part B), open-label, multicenter study evaluating the PK, safety, and tolerability of multiple doses of tezacaftor (TEZ; VX-661) in combination with ivacaftor (IVA; VX-770) in subjects 6 through 11 years of age with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation.

Part A has been completed before initiation of Part B, and the data have been analyzed based on a separate SAP for Part A (version 1.0, dated 11 January 2017).

The pharmacokinetic (PK) of TEZ/IVA also will be evaluated in the study. The relevant PK analyses will be documented separately in the clinical pharmacology analysis plan (CPAP) for the study.

The Vertex Biometrics Department or designee will perform the analysis of Part B safety and efficacy data as defined in this plan; SAS (Version 9.4 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the final clinical data lock. If the methods in this SAP differ from the methods described in the protocol, the SAP prevails. Unless otherwise specified, Study VX15-661-113 in the rest of this document pertains to Study VX15-661-113 Part B.

5 STUDY OBJECTIVES FOR PART B

5.1 Primary Objective

To evaluate the safety and tolerability of VX-661 in combination with ivacaftor through Week 24

5.2 Secondary Objectives

- To evaluate the PK of VX-661, M1-661, M2-661, ivacaftor, M1-ivacaftor, and M6-ivacaftor after administration of multiple doses of VX-661 in combination with ivacaftor
- To evaluate the efficacy of VX-661 in combination with ivacaftor through Week 24

6 STUDY ENDPOINTS FOR PART B

6.1 Primary Endpoints

Safety and tolerability of VX-661 in combination with ivacaftor as determined by adverse events (AEs), clinical laboratory values (serum chemistry, hematology, coagulation studies, lipids, vitamins, and urinalysis), standard 12-lead electrocardiograms (ECGs), vital signs, pulse oximetry, ophthalmologic examinations, and spirometry

6.2 Secondary Endpoints

- VX-661, M1-661, M2-661, ivacaftor, M1-ivacaftor, and M6-ivacaftor PK parameters, including C_{max}, AUC_{τ}, and other PK parameters as appropriate
- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline through Week 24
- Relative change in $ppFEV_1$ from baseline through Week 24
- Absolute change in weight and weight-for-age z-score from baseline at Week 24
- Absolute change in height and height-for-age z-score from baseline at Week 24
- Absolute change in body mass index (BMI) and BMI-for-age z-score from baseline at Week 24
- Absolute change in sweat chloride from baseline through Week 4
- Absolute change in sweat chloride from baseline through Week 24
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline through Week 24

[redacted]

7 STUDY DESIGN

7.1 Overview of Study Design

This is a Phase 3, 2-part (Part A and Part B), open-label, multicenter study evaluating the PK, safety, and tolerability of multiple doses of VX-661 in combination with ivacaftor in subjects 6 through 11 years of age with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation. Efficacy will also be evaluated in Part B. This SAP describes the analysis plan for Part B, but a description of Part A study design is included below for reference.

Part A is composed of 2 weight-based cohorts, which will be enrolled simultaneously, and Part B is composed of a single cohort. Subjects who participated in Part A and are eligible to participate in Part B if Part B eligibility criteria are met. All genotypes listed in Section 16 of the protocol are eligible in **Part A**. Each genotype for which clinical benefit has been demonstrated in the corresponding adult population are eligible in **Part B,** please see details in the protocol.

Part A (Completed)

Up to approximately 16 subjects total were planned for enrollment across Cohort 1 (subjects weighing <25 kg at baseline) and Cohort 2 (subjects weighing ≥25 kg at baseline).

Part A included the following:

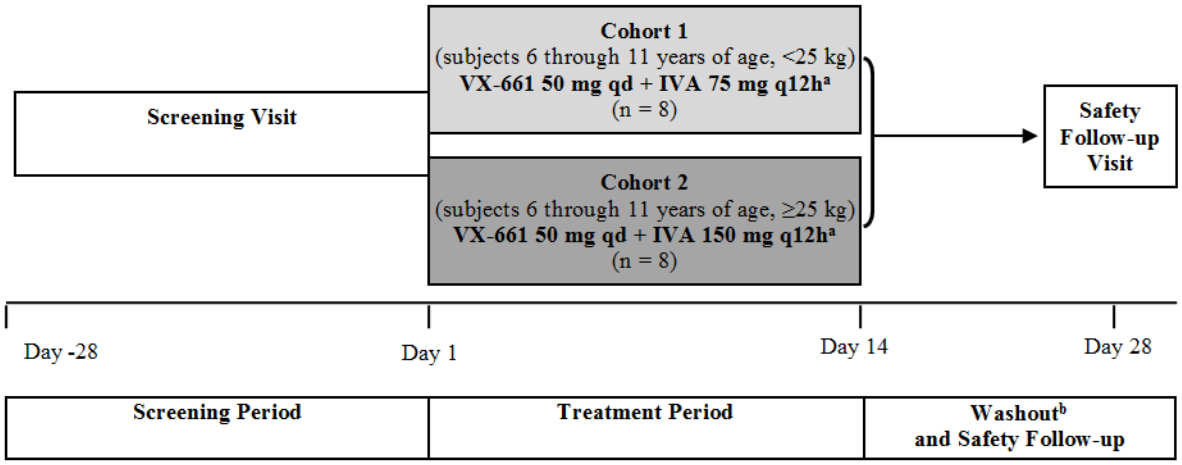
- Screening Period (Day -28 through Day -1)
- Treatment Period (Day 1 through Day 14)

- Washout Period (Day 14 to Day 28 [± 3 days])
- Safety Follow-up Visit (14 [± 3] days after the last dose of study drug)

Figure 7-1 depicts the schematic for the Part A study design. After obtaining written informed consent (and assent, if applicable), Screening Visit assessments were completed at any time during the period of 4 weeks (Day -28 through Day -1) before the first dose of the study drug (Day 1). During the Treatment Period, subjects were administered VX-661 50 mg daily (qd) in combination with ivacaftor, either 75 mg (subjects <25 kg at baseline) or 150 mg (subjects ≥25 kg at baseline), every 12 hours (q12h) for 14 days. A 2-week Washout Period (Day 14 to Day 28 [± 3 days]) were included in order to evaluate the off-drug response. A Safety Follow-up Visit is scheduled to occur 14 (± 3) days after the last dose of study drug for all subjects, including subjects who permanently discontinue from study treatment for any reason.

A review of safety, tolerability, and PK data has been completed by an internal Vertex team after Part A to select the VX-661 dose for Part B.

Figure 7-1 Schematic of Study Design for Part A



IVA: ivacaftor; n: number of subjects; q12h: every 12 hours; qd: daily.
Note: Approximately 16 subjects (approximately 8 subjects in each cohort) are planned for enrollment.
[a] Weight refers to weight at baseline. Study drug will be administered from Day 1 through Day 14. On Day 14, only the morning dose of study drug will be administered.
[b] A 2-week Washout Period (Day 14 to Day 28 ± 3 days) will be included in order to evaluate the off-drug response.

Part B

Approximately 56 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 50 subjects are expected to complete Part B.

Part B includes the following:

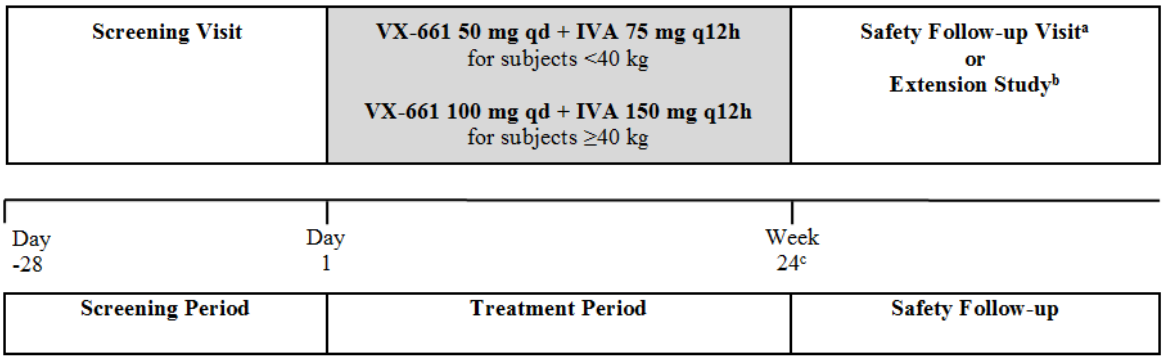
- Screening Period (Day -28 through Day -1)
- Treatment Period (Day 1 through Week 24 [± 5 days])
- Safety Follow-up Visit (4 weeks [± 7 days] after the last dose of study drug)

Figure 7-2 of protocol depicts the schematic for the Part B study design. After obtaining written informed consent (and assent, if applicable), Screening Visit assessments will be completed at any time during the period of 4 weeks (Day -28 through Day -1) before the first dose of study

drug (Day 1). During the Treatment Period, subjects will be administered VX-661 50 mg qd in combination with ivacaftor 75 mg q12h (subjects <40 kg at baseline) or VX-661 100 mg qd in combination with ivacaftor 150 mg q12h (subjects ≥40 kg at baseline) for 24 weeks. No dose adjustments will be made throughout the duration of treatment in this study. At the Week 24 Visit, subjects who complete study drug treatment will be offered the opportunity to enroll in an extension study evaluating VX-661 in combination with ivacaftor (enrollment will be based on the eligibility criteria specified within the extension study). Subjects who prematurely discontinue study drug treatment are not eligible to rollover into the extension study.

A Safety Follow-up Visit is scheduled to occur 4 weeks (± 7 days) after the last dose of study drug. The Safety Follow-up Visit is not required for subjects who have enrolled in the extension study within 28 days after the last dose of study drug. Subjects who permanently discontinue study drug treatment will have an Early Treatment Termination (ETT) Visit and a Safety Follow-up Visit.

Figure 7-2 Schematic of Study Design for Part B



IVA: ivacaftor; q12h: every 12 hours; qd: daily.
Note: Weight refers to weight at baseline.
[a] The Safety Follow-up Visit will occur 4 weeks [± 7 days] after last dose and is not required for subjects who have enrolled in the extension study within 28 days after the last dose of study drug.
[b] At the Week 24 Visit, subjects who complete study drug treatment will be offered the opportunity to enroll in an extension study evaluating VX-661 in combination with ivacaftor. Subjects who prematurely discontinue study drug treatment are not eligible to rollover into the extension study.
[c] The last dose of study drug will be the evening dose administered the day before the Week 24 Visit.

7.2 Sample Size and Power for Part B

Planned enrollment is approximately 56 subjects. Assuming a 10% dropout rate, approximately 50 subjects are expected to complete Part B. An important safety endpoint is the incidence of AEs. With a total sample size of 50 subjects (completer), there is a 92.3% chance of observing AEs in at least 1 subject if the true incidence rate is 5%, and a 99.5% chance of observing AEs in at least 1 subject if the true incidence rate is 10%. The probabilities have been calculated by assuming a binomial distribution for the number of AEs using SAS®.

7.3 Randomization for Part B

Not applicable.

7.4 Blinding and Unblinding for Part B

Not applicable because this is an open-label study.

8 ANALYSIS SETS FOR PART B

The following analysis sets are defined: Safety Set, Full Analysis Set, [redacted]

The **Safety Set** is defined as all subjects who received at least 1 dose of study drug in Part B of the study.

The **Full Analysis Set** is defined as all subjects who carry the intended *CFTR* mutations and received at least 1 dose of study drug in Part B of the study. [redacted]

9 STATISTICAL ANALYSIS FOR PART B

9.1 General Considerations

All individual subject data for those who enrolled or received at least one dose of study drug in Part B, will be presented in data listings. The Schedule of Assessments is provided in Section 3 of the protocol. The precision standards are provided in Section 12.3.

Continuous variables will be summarized using the following descriptive summary statistics: 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.

Treatment-emergent (TE) period will correspond to data from the first dose of study drug to 28 days after the last dose of the study drug or to the completion of study participation date, whichever occurs first. Completion of study participation is defined as one of the following:

- For subjects who complete Part B and enroll in the extension study within 28 days of the Week 24 Visit: the last participation date
- For subjects who complete Part B and do not enroll in the extension study within 28 days of the Week 24 Visit: the Safety Follow-up Visit
- For subjects who prematurely discontinue study drug treatment but do not withdraw consent: the latest of ETT Visit, or Safety Follow-up Visit (if required)
- For subjects who withdraw consent: date of withdrawal of consent

Baseline for Part B is defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in Part B. For ECGs, baseline will be the average of the 3 pretreatment measurements on Day 1 of Part B. For sweat chloride, the baseline value will be the mean of the last values on the left and the right arm prior to the first dose of the study.

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

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

Unscheduled Visits: Subject data obtained during unscheduled visits will not be summarized but will be included in subject data listings only, except for the analysis of the maximum value during TE period and maximum changes from baseline during TE period (see Section 9.4.3).

Visit Windowing Rules: Section 12.2 defines the windows for protocol-defined visits. The windows will be applied using the following rules for both scheduled and unscheduled visits:

1. If no measurement is available within a visit window, the assessment will be considered missing for the visit;
2. If there is more than one measurement available within the same visit window, use the following rules:

- For all efficacy parameters, if there are multiple measurements within a visit window, the record at the scheduled visit will be used. Otherwise,
  - The record closest to the target day will be used;
  - If there are multiple records with the same distance to the target day, the latest record will be used.
  - Assessments at early treatment termination (ETT) visit will follow the windowing rules for regular visits up to Week 24.
  - Assessments at safety follow-up (SFU) visit will follow the windowing rules for regular visits if they fall within the upper boundary of the window for Week 24, or remain as SFU if they go beyond the upper boundary of the window for Week 24.
- For all safety parameters, if there are multiple measurements within a visit window, then
  - the record closest to the target day will be used;
  - if there are multiple records within the same distance from the target day, the latest record will be used; or
  - SFU visit will not be windowed; instead, it will be used according to the nominal visit in relevant analyses.

Note, spirometry assessments, BMI, weight, and height will be used for both efficacy and safety purposes. Their measurements will follow the visit windowing rules for efficacy parameters.

Incomplete/Missing data will not be imputed, unless otherwise specified.
Outliers: No formal statistical analyses will be performed to detect or remedy the presence of statistical outliers, unless otherwise specified.

9.2 Background Characteristics for Part B

9.2.1 Subject Disposition

In the summary table of subject disposition, the number of subjects in the following categories will be presented:

- Safety Set
- Full Analysis Set

[redacted]

In the same table, the number and percentage (based on FAS) of subjects in each of the following disposition categories will be presented:

- Completed study drug treatment
- Prematurely discontinued the treatment (TEZ or IVA) and the reasons for discontinuations
- Completed study
- Prematurely discontinued study and the reasons for discontinuations

A listing will be provided for subjects who discontinued treatment or who discontinued study with reasons for discontinuations.

9.2.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics data will be summarized based on the Safety Set.

Demographic data will include the following:

- Age at screening
- 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, and Other)

Baseline characteristics will include the following, all at baseline unless otherwise specified:

- Type of mutation (F508del/F508del; F508del/Residual Function)
- Weight (kg) at baseline and weight group at enrollment
- Weight z-score
- Height (cm)
- Height z-score
- BMI (kg/m^2)
- BMI z-Score
- FEV_1
- $ppFEV_1$
- Sweat Chloride
- CFQ-R respiratory domain score

[redacted]

9.2.3 Medical History

Medical history in this study will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA).

Based on the Safety Set, medical history will be summarized descriptively by system organ class (SOC) and preferred term (PT). The corresponding data listing will also be provided.

In addition, a listing of subjects reported to have had positive cultures for respiratory pathogens in 2 years prior to screening (i.e., answered yes on the respiratory microbiology form) will be presented. A listing of ophthalmology history will also be presented.

9.2.4 Prior and Concomitant Medications

Medications used in this study will be coded using the World Health Organization Drug Dictionary Enhanced (WHODD) and categorized as follows:

- **Prior medication**: any medication that started before the first dose of study drug in Part B, regardless of when it ended.
- **Concomitant medication**: medication continued or newly received during the TE period for Part B.
- **Post-treatment medication**: medication continued or newly received after the TE period for Part B. For those subjects from Part A who enrolled in Part B, medications that continued or were newly received on or after the first dose of study drug in Part B will not be considered as post-treatment medication.

A given medication can 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 a missing or partially missing start/end date or time and it cannot be determined whether the medication was taken before initial dosing, concomitantly, or post-treatment, it will be considered as prior, concomitant, and post-treatment.

Based on the Safety Set, concomitant medications will be summarized descriptively by: 1) preferred name (PN); and 2) anatomic class (ATC) level 1, ATC level 2, and preferred name. Prior medications and post-treatment medications will be listed for each subject.

As an intermediate step for programming purposes, medications with missing or partially missing start dates will use 2000 to impute for the missing year, January for the missing month, and 1 for the missing day. Medications with missing or partially missing stop dates will use 2050 to impute for the missing year, December for the missing month, and the last day of the month for the missing day. The logic to decide the category of a medication is presented in Table 9-1:

Table 9-1 Logic for Determining the Category of a Medication

	Medication end date		
Medication start date	< first dose date of study drug	≥ first dose date and ≤ End date of TE period	> End date of TE period
< first dose date of study drug	P	PC	PCA
≥ first dose date and ≤ End date of TE period	-	C	CA

> End date of TE period	-	-	A

P: Prior; C: Concomitant; A: Post

9.2.5 Study Drug Exposure

Exposure summaries will be presented based on the Safety Set.

Duration of study drug exposure is defined as follows: last dose date in Part B – first dose date in Part B + 1 day, regardless of any interruption in dosing between the first and the last dose.

Duration of study drug exposure will be summarized descriptively (number, mean, SD, median, minimum, and maximum).

9.2.6 Study Drug Compliance

Study drug compliance based on study drug exposure will be calculated as: $100 \times [1 - (\text{total number of days of any study drug interruption}) / (\text{duration of study drug exposure in days})]$.

Study drug compliance will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. Compliance also will be summarized in categories: <80% and ≥80% using frequency tables.

Study drug compliance will be summarized based on the Safety Set.

9.2.7 Important Protocol Deviations

Important protocol deviations (IPD) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/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 database lock.

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

- Violation of subjects rights, safety or well-being
- Subject entered the study despite violation of any inclusion or exclusion criteria
- Subject was less than 80% compliant with study medications
- Subject received excluded concomitant medications
- Subject received the wrong treatment or incorrect doses
- Subject remained in study despite meeting withdrawal criteria

Occurrence of any of these events should be considered as potential IPDs.

IPDs (from the clinical database or from the site deviation log) will be presented in an individual subject data listing.

9.3 Efficacy Analysis for Part B

There is no multiplicity adjustment in this study; p-values provided for the secondary and other endpoints are considered nominal.

All efficacy analyses described in this section will be based on the Full Analysis Set, unless specified otherwise. The analysis will include all available measurements through the last assessment, including measurements after treatment discontinuation.

9.3.1 Analysis of Secondary Efficacy Variables

Absolute change from baseline in percent predicted FEV_1 through Week 24

This endpoint is the average absolute change from baseline in percent predicted FEV_1 (with a unit of percentage points) through Week 24, which is defined as the average of absolute changes from baseline in ppFEV1 at each post-baseline scheduled visits.

Percent predicted FEV_1 is the ratio of FEV_1 (L) to the predicted FEV_1 (L), expressed as a percentage. The predicted FEV_1 will be calculated using the Quanjer GLI-2012 Regression Equations and Lookup Tables[1], adjusting for age, height, sex and ethnicity. Details are provided in Appendix 12.6.

Absolute change from baseline in $ppFEV_1$ will be analyzed using a restricted maximum likelihood (REML)-based mixed effect model repeated measures (MMRM) approach that would include visit and baseline $ppFEV_1$(continuous) as fixed effects, and subject as random effect. An unstructured (co)variance structure will be used to model the within-subject errors. If the model fails to converge, a compound symmetry covariance structure will be considered. The degrees of freedom of the denominator will be approximated by the Kenward-Roger's method.[2]

The primary result obtained from the model will be the average treatment effect through Week 24. The corresponding LS means, standard error (SE), the 95% CI, and p-value will be provided.

Furthermore, absolute change from baseline in percent predicted FEV_1 at each post-baseline will be estimated from the main model above. The LS means with the corresponding 2-sided 95% CIs and p-value will be provided at Week 24; LS means and the corresponding 2-sided 95% CIs will be provided for other post-baseline scheduled visits.

Relative change in percent predicted FEV_1 from baseline through Week 24

A similar MMRM model as that for absolute change in ppFEV1 from baseline through Week 24 will be used for this variable using the same approach as described for the absolute change in $ppFEV_1$ from baseline.

Absolute change in weight (/weight-for-age z-score) from baseline at Week 24

Absolute change in height (/height-for-age z-score) from baseline at Week 24

Absolute change in BMI (/BMI-for-age z-score) from baseline at Week 24 (details of BMI-for-age z-score in section 12.4)

A similar MMRM model will be used for the above variables using the same approach as described for the absolute change in ppFEV1 from baseline through Week 24. The MMRM will include corresponding baseline values (continuous) as covariate instead of baseline $ppFEV_1$. For these variables, the assessment of efficacy will be primarily based on the estimated mean change from baseline at Week 24.

Absolute change in sweat chloride from baseline through Week 4 and through Week 24

A similar MMRM model will be used for this variable using the same approach as described for the absolute change in $ppFEV_1$ from baseline. The MMRM will include baseline sweat chloride value as covariate instead of baseline $ppFEV_1$. Please note that the first post-baseline assessment

of sweat chloride is at Week 4, thus, the estimated mean change at Week 4 will be used to assess absolute change in sweat chloride from baseline through Week 4.

Absolute change in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score from baseline through Week 24

A similar MMRM model will be used for this variable using the same approach as described for the absolute change in $ppFEV_1$ from baseline. The MMRM will include the baseline CFQ-R respiratory domain score as a covariate instead of baseline $ppFEV_1$.

[redacted]

9.4 Safety Analysis for Part B

Safety is a primary objective of this study. Safety analysis will be based on the Safety Set. Only descriptive analysis of safety will be performed (i.e., no statistical hypothesis testing will be performed). The safety endpoints will be summarized using descriptive summary statistics. The primary analysis of safety will be based on the overall, in addition, by-dose level summary is provided. Due to the small sample size, the by-dose level summary should be interpreted with caution.

The safety endpoints included for analyses are as follows:

- Treatment-emergent adverse events (TEAEs)

- Clinical laboratory measurements (chemistry, hematology, coagulation, lipids, vitamins, and urinalysis)
- Standard 12-lead ECG
- Vital signs
- Pulse oximetry
- Ophthalmologic examinations
- Spirometry

Throughout this section, "change" refers to absolute change from baseline.

9.4.1 Adverse Events

AEs will be coded according to MedDRA and categorized as pretreatment AEs, TEAEs, or post-treatment AEs:

- **Pretreatment AE:** any AE that started before the first dose of study drug in Part B.
- **TEAE:** any AE that increased in severity or that was newly developed during the TE period for Part B.
- **Post-treatment AE:** any AE that increased in severity or that was newly developed beyond the TE period for Part B.

For AEs with missing or partial start dates, if there is no clear evidence that the AEs started (or increased in severity) before or after study treatment for Part B, then the AEs will be classified as TEAEs. As an intermediate step for programming purposes, imputation rules for missing or partially missing AE start/end dates are defined in Section 12.5.

AE summary tables will be presented for TEAEs only and will include the following:

(1) all TEAEs

(2) related (defined as possibly related, related, or missing) TEAEs

(3) serious TEAEs

(4) Grade 3/4 TEAEs

(5) TEAEs leading to treatment discontinuation

(6) TEAEs leading to treatment interruption

Summaries will be presented by MedDRA SOC and PT using frequency counts and percentages. A subject with multiple occurrences of the same TEAE or a continuing TEAE will be counted only once.

9.4.1.1 Overview of TEAEs

An overview of all TEAEs will be provided for the total number of TEAEs, and with number and percent of subjects including the following categories:

- Any TEAEs
- TEAEs by strongest relationship

- Related TEAEs
- TEAEs by maximal severity
- Grade 3/4 TEAEs
- Serious TEAEs
- Related Serious TEAEs (possibly related, related or missing)
- TEAEs leading to treatment discontinuation (this will include TEAEs leading to discontinuation of either TEZ tablet or the IVA tablet)
- TEAEs leading to treatment interruption (this will include TEAEs leading to interruption of either TEZ tablet or the IVA tablet)
- TEAEs leading to death

In addition, a listing containing individual subject adverse event data for TEAEs leading to treatment discontinuation, treatment interruptions, SAEs and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.

For all AEs, the action taken on the CRF for TEZ/IVA (AM dose) is collected separately from the AE action taken for IVA (PM dose). As a result, it is possible that in the AE dataset, the AE actions taken for the two agents are different. The summary of TEAE Leading to Treatment Discontinuation or Interruptions account for discontinuation and interruptions for either agent.

9.4.1.2 TEAEs by System Organ Class (SOC) and Preferred Term (PT)

Summaries will be presented by MedDRA system organ class (SOC) and preferred term using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries.

9.4.1.3 Respiratory Events and Symptoms

Respiratory symptoms are defined as any TEAEs for the following 3 PTs:

- Chest discomfort
- Dyspnoea
- Respiration abnormal

Respiratory events are defined as any of the afore-mentioned respiratory symptoms, or any TEAEs for the following 4 additional PTs:

- Asthma
- Bronchial hyperreactivity
- Bronchospasm
- Wheezing

A summary of respiratory symptoms and events will be presented by preferred term.

9.4.2 Clinical Laboratory

For treatment-emergent laboratory measurements, the raw values and change from baseline values of the continuous hematology, chemistry, vitamin, lipids and coagulation results will be summarized in SI units at each scheduled time point.

The number and percentage of subjects with events meeting threshold criteria laboratory event during the TE period will be summarized, including the shift of the event meeting threshold criteria from baseline to post-baseline. The threshold criteria are provided in section12.6.

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

In addition, a listing containing individual subject hematology, chemistry, vitamin, lipids and coagulation results outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled visits.

For each liver function test (LFT) laboratory test (i.e. alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin), the following additional analyses will be presented:

- A listing of subjects with elevated LFT results during the TE period will be presented. For each subject in the listing, LFT assessments at all time points will be included (scheduled and unscheduled).
- For each of the LFTs, mean values (±SD) will be plotted by visit, and a box plot of the LFT value/ULN will be plotted by visit.
- The incidence of LFTs meeting threshold criteria
- For each of the LFTs, mean values (±SD) will be plotted by visit, and a box plot of the LFT value/ULN will be plotted by visit.
- The incidence of LFTs meeting threshold criteria against the baseline threshold criteria also will be summarized by LFT parameters and visit (only shifts to values worse than baseline will be presented).

A summary table for the shift from baseline to the value at Week 24 will be provided for vitamin levels and lipid panel. A box plot of vitamin levels and lipid panel also will be plotted against visit.

9.4.3 Standard 12-Lead Electrocardiogram

For treatment-emergent ECG measurements, a summary of raw values and change from baseline values will be provided at each scheduled time point for the following standard 12-lead ECG measurements: PR, QTc for HR intervals (QTcF), QRS duration, and HR.

The number and percentage of subjects with at least 1 ECG event meeting threshold criteria during the TE period will be summarized by ECG parameters. The threshold criteria are provided in Appendix 12.6.

For QTcF and HR, mean values (±SD) will be plotted by scheduled visit.

9.4.4 Vital Signs

For treatment-emergent vital signs measurements, the raw values and change from baseline values will be summarized at each scheduled time point for the following: systolic and diastolic blood pressure (mm Hg), body temperature (^{o}C), HR (beats per minute), and respiratory rate (breaths per minute).

The number and percentage of subjects meeting threshold criteria during the TE period will be summarized by vital signs parameters. The threshold criteria are provided in Appendix 12.6.

For SBP and DBP, mean values (±SD) will be plotted by scheduled visit.

9.4.5 Physical Examination

Physical examination findings will be presented as a data listing only.

9.4.6 Other Safety Analyses

9.4.6.1 Pulse Oximetry

For treatment-emergent percent of oxygen saturation by pulse oximetry, a summary of raw values and change from baseline values will be provided at each scheduled time point. In addition, the mean value of percent of oxygen saturation at each visit during the TE Period will be plotted.

9.4.6.2 Ophthalmologic Examination

Ophthalmologic examination findings will be presented as a data listing.

9.4.6.3 Spirometry

The number and percentage of subjects with percent predicted FEV1 decline ≥10, ≥15, and ≥20 percentage points in the absolute change from baseline in predose value will be summarized for scheduled visits.

In addition, the number and percentage of subjects with ⩾0.10 L or ⩾0.20 L decrease in the absolute change from baseline through Week 24 for FEV_1 will also be summarized for scheduled visit.

Subjects with ≥10 percentage points decrease in absolute change from baseline through Week 24 for $ppFEV_1$ or ≥0.10 L decrease in the absolute change from baseline through Week 24 for FEV_1 will be listed.

10 SUMMARY OF PLANNED INTERIM ANALYSIS

Not Applicable.

11 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.

[2] Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 1997;53:983-97.

[3] Centers for Disease Control and Prevention. CDC Growth Charts. Available at: http://www.cdc.gov/growthcharts/percentile_data_files.htm.

12 APPENDICES

12.1 Schedule of Assessments

Please see Section 3.0 Schedule of Assessments of the protocol.

12.2 Analysis Visit Window Mapping Rules for Efficacy and Safety Measurement

Table 12-3 Visit Window Mapping Rules

Assessments	Visit	Target Study Day	Visit Window (in study days)
• Weight and height • Pregnancy test • Standard 12-lead ECG • Vital signs • Pulse oximetry • Spirometry • Labs o Chemistry o Hematology • CFQ-R	Day 1	1	[1, 1]
	Day 15	15	[2, 22]
	Week 4	29	[23, 43]
	Week 8	57	[44, 85]
	Week 16	113	[86, 141]
	Week 24	169	[142, 183]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up Visit (no CFR-Q)	N/A	Nominal
• Lipid panel			
	Day 1	1	[1,1]
	Week 8	57	[2, 85]
	Week 16	113	[86, 141]
	Week 24	169	[142, 183]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
• Sweat chloride [redacted]	Day 1	1	[1, 1]
	Week 4	29	[2, 99]
	Week 24	169	[100, 183]
• Vitamin levels	Day 1	1	[1, 1]
	Week 8	57	[2, 113]
	Week 24	169	[114, 183]
	ETT	NA	Follow the individual visit window to be mapped to individual visits
• Labs o Coagulation o Urinalysis	Day 1	1	[1, 1]
	Week 24	169	[2, 183]
	ETT	NA	Follow the individual visit window to be mapped to individual visits

	Safety Follow-up Visit	N/A	Nominal

Note:

1. To apply the above visit windows, please first determine the baseline measurements based on the first dose of study medication and then label Day 1 for the date of the first dose of study drug, and use the nominal visit names to label SFU (for safety).

2. After baseline, and SFU (for safety) measurements are determined; the above visit windows will be applied to determine the analysis visit names for all remaining measures at scheduled or unscheduled visits.

3. If there is no scheduled Day 1 post dose visit, any assessments on Day 1 after the first dose will be considered for the window of next visit.

4. For all efficacy parameters, if there are multiple measurements within a visit window, the record at the scheduled visit will be used.

    - If there are no measurements at the scheduled visit, then the record closest to the target day will be used;

    - If there are multiple records with the same distance to the target day, the latest record will be used.

5. For all safety parameters, if there are multiple measurements within a visit window, then 1) the record closest to the target day will be used; or 2) if there are multiple records within the same distance from the target day, the latest record will be used.

6. FEV_1, $ppFEV_1$, BMI, Weight and Height are following the efficacy windowing rules.

<u>Special handling for ECG:</u>

- On Day 1, the pre-dose measurements will be collected as triplets, the average of the triplicate will be used as pre-dose measurement on Day 1. Only pre-dose measurement with nominal visit names related to the triplets shall be used in this average.

For other post-dose visits, the visit window in the above table will apply.

12.3 Standards for Safety and Efficacy Variable Display in TFLs

Continuous Variables

The precision for continuous variables has been specified in the Vertex Standard Programming Rules document (Version 1.0, December 2015):

[redacted]

Categorical Variables: Percentages will be presented to 1 decimal place.

12.4 BMI-for-age z-score

BMI z-score will be calculated by using Centers for Disease Control and Prevention (CDC) growth charts[3]. The BMI z-score will be calculated as follows:

$$z = \begin{cases} \dfrac{\left(\dfrac{X}{M}\right)^{L} - 1}{LS}, & L \neq 0 \\ \dfrac{\ln\left(\dfrac{X}{M}\right)}{S}, & L = 0 \end{cases}$$

where X is the derived BMI value in kg/m^2 based on the raw weight and raw height and L, M, and S are selected from the CDC BMI-for-age chart by subject sex and age. The BMIAGE file contains these parameters by sex (1=male, 2=female) and age; it is available at: http://www.cdc.gov/growthcharts/percentile_data_files.htm. SAS code for calculating percentiles and z-scores is available at: http://www.cdc.gov/growthcharts/computer_programs.htm.

NOTE: The CDC BMI-for-age charts are designed for use in pediatric populations (2 to 20 years of age); in this analysis plan, BMI z-score will be calculated only for subjects between 2 and <20 years of age at screening.

12.5 Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined below:

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, TEAE or post-treatment AE.

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, TEAE or post-treatment AE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site 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.

12.6 Details of GLI Equations for Calculating ppFEV$_1$

Percent predicted values will be calculated for parameters of FEV_1, FVC, FEV_1/FVC, and $FEF_{25\%-75\%}$ using the Quanjer GLI-2012 Regression Equations and Lookup Tables.

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

Quanjer GLI-2012 Regression Equations and Lookup Tables. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 7 April 2013. Available at:

http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/quanjer-gli-2012-regression-equations-and-lookup-tables.aspx

Accessed Sep 11, 2017.

The instructions and tools on how to implement the Quanjer GLI-2012 equations are:

Implementing GLI-2012 regression equations. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 19 July 2015. Available at:

http://www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools/it-engineers-and-manufacturers.aspx

Accessed Sep 11, 2017.

GLI-2012 - SAS Macro. Sanja Stanojevic. Version 2, 7 April 2013. Available at:

http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/sas-macro.aspx

Accessed Sep 11, 2017.

Data handling rule for spirometry is as follows:

- Input age with at least 2 decimal places, and height with 1 decimal place.
- For race, map CRF black or AA to black, all other races in CRF (except white) are mapped to 'other'; white is a reference race in the equations and assumes 0 values for all race coeffiecients in the GLI equations.

12.7 Threshold Analysis Criteria

Threshold Criteria for Clinical Chemistry and Hematology

Parameter	Threshold Criteria	Comments
Clinical Chemistry		
CPK	>ULN - ≤ 2.5 x ULN >2.5 - ≤ 5 x ULN >5 - ≤ 10x ULN >10 x ULN	CTCAE grades 1-4
Creatinine	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	CTCAE grades 1-4
Blood Urea Nitrogen	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	Same criteria as creatinine No CTCAE
Sodium	Hyponatremia <LLN - ≥130 mmol/L <130 – ≥120 mmol/L <120 mmol/L	CTCAE grade 1, 3, 4 (No CTCAE grade 2)
	Hypernatremia >ULN - ≤ 150 mmol/L >150 mmol/L- ≤155 mmol/L >155 mmol/L - ≤ 160 mmol/L >160 mmol/L	CTCAE grade 1-4
Potassium	Hypokalemia <LLN – ≥ 3.0 mmol/L <3.0 – ≥ 2.5 mmol/L <2.5 mmol/L	CTCAE grade 1&2, 3, 4 (Grade 1 and 2 are the same)
	Hyperkalemia >ULN – ≤ 5.5 mmol/L >5.5 – ≤ 6.0 mmol/L >6.0 – ≤ 7.0 mmol/L >7.0 mmol/L	CTCAE grade 1-4
Total Cholesterol	>ULN – ≤ 7.75 mmol/L >7.75 – ≤ 10.34 mmol/L >10.34 – ≤ 12.92 mmol/L >12.92 mmol/L	CTCAE grade 1-4
Triglycerides	>1.71 – ≤ 3.42 mmol/L >3.42 – ≤ 5.7 mmol/L >5.7 – ≤ 11.4 mmol/L >11.4 mmol/L	CTCAE grade 1-4
Glucose	Hypoglycemia <LLN – ≥ 3.0 mmol/L <3.0 – ≥ 2.2 mmol/L <2.2 - ≥ 1.7 mmol/L <1.7 mmol/L	CTCAE grade 1-4
	Hyperglycemia >ULN - ≤ 8.9 mmol/L >8.9 – ≤ 13.9 mmol/L >13.9 – ≤ 27.8 mmol/L >27.8 mmol/L	CTCAE grade 1-4
Albumin	<35 - ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3

Amylase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4
Lipase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4
Direct bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	Same Criteria as Total Bilirubin No CTCAE Not in DILI Guidance
GGT	>ULN - ≤ 2.5 x ULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	CTCAE grade 1-4
Calcium	Hypercalcemia >ULN - ≤ 2.9 mmol/L >2.9 – ≤ 3.1 mmol/L >3.1 – ≤ 3.4 mmol/L >3.4 mmol/L	CTCAE grade 1-4
	Hypocalcemia <LLN - ≥ 2.0 mmol/L <2.0 – ≥1.75 mmol/L <1.75 – ≥ 1.5 mmol/L <1.5 mmol/L	CTCAE grade 1-4
Magnesium	Hypermagnesemia >ULN - ≤ 1.23 mmol/L >1.23 – ≤ 3.30 mmol/L >3.30 mmol/L	CTCAE grade 1, 3, 4 No CTCAE grade 2
	Hypomagnesemia <LLN - ≥ 0.5 mmol/L <0.5 – ≥ 0.4 mmol/L <0.4 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
Inorganic phosphate	Hypophosphatemia <LLN - ≥ 0.8 mmol/L <0.8 – ≥.6mmol/L <0.6 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
ALT	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN >5 – ≤ 8 xULN >8 – ≤ 20.0 xULN >20.0 x ULN	Per FDA DILI Guidance Jul 2009 and CTCAE
AST	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN >5 – ≤ 8 xULN >8 – ≤ 20.0 xULN >20.0 x ULN	FDA DILI Guidance and CTCAE
ALT or AST	(ALT>ULN and ALT ≤ 3 xULN) or (AST>ULN and AST≤ 3 xULN) (ALT>3 xULN and ALT ≤ 5 xULN) or (AST>3xULN and AST≤ 5 xULN)	FDA DILI Guidance

	(ALT>5 xULN and ALT ≤ 8 xULN) or (AST>5xULN and AST≤ 8 xULN) (ALT>8 xULN and ALT ≤ 20 xULN) or (AST>8xULN and AST≤ 20 xULN) ALT>20 xULN or AST> 20 xULN	
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 and CTCAE
Total Bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	FDA DILI Guidance and CTCAE
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	FDA DILI Guidance Jul 2009
Hematology		
WBC	WBC decreased <LLN - ≥ 3.0 x 10e9 /L <3.0 – ≥ 2.0 x 10e9 /L <2.0 – ≥ 1.0 x 10e9 /L <1.0 x 10e9 /L	CTCAE grade 1-4
	Leukocytosis >100 x 10e9 /L	CTCAE grade 3 (only Grade available)
Lymphocytes	Lymphocyte decreased <LLN - ≥ 0.8 x10e9 /L <0.8 – ≥ 0.5 x10e9 /L <0.5 – ≥ 0.2 x10e9 /L <0.2 x10e9 /L	CTCAE grade 1-4
	Lymphocyte increased >4 – ≤ 20 x10e9/L >20 x10e9/L	CTCAE grade 2, 3 (only Grades available)
Neutrophils	Neutrophil decreased <LLN - ≥ 1.5 x10e9 /L <1.5 – ≥ 1.0 x10e9 /L <1.0 – ≥ 0.5 x10e9 /L <0.5 x10e9 /L	CTCAE grade 1-4
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

Threshold Criteria for Coagulation

Parameter	Threshold	Comments
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

Threshold Criteria for ECGs

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ECGs
Ref.: CPMP 1997 guideline.

Parameter	Threshold	Comments
HR	Bradycardia	Per HV grade 2, 3, plus shift change
	<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	
	Tachycardia	Per HV grade 1, 2, 3, plus shift change
	>100 bpm	
	>115 bpm	
	>130 bpm	
	Increase from baseline ≥10 bpm	
	Increase from baseline ≥20 bpm	
	>100 bpm and increase from baseline ≥10 bpm	
	>100 bpm and increase from baseline ≥20 bpm	
PR	≥240 ms	
	≥300 ms	
	≥200 ms and increase from baseline ≥40 ms	
	≥200 ms and increase from baseline ≥100 ms	
QRS	>110 ms	
	>160 ms	
	Increase from baseline ≥20 ms	
	Increase from baseline ≥40 ms	
QTc	>450 ms (Male)	
	>470 ms (Female)	
	≥500 ms	
	Increase from baseline >10 ms	
	Increase from baseline >20 ms	
	Increase from baseline >40 ms	
	Increase from baseline >60 ms	

Threshold Criteria for Vital Signs

Parameter	Threshold Criteria	Comments
HR	Same PCS as above in ECG category	
SBP	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	
DBP	DBP increased	809/770 analyses
	>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	CTCAE grade 1-3
	≥5 % increase from baseline	
	≥10 % increase from baseline	
	≥ 20% increase from baseline	

Weight loss ≥5 % decrease from baseline ≥10 % decrease from baseline ≥ 20% decrease from baseline	CTCAE grade 1-3