VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan

Module 1: Methods

Protocol Number VX15-661-112

A Phase 2, Randomized, Placebo-Controlled, Double-blind Study to Evaluate the Effect of VX-661 in Combination With Ivacaftor on Chest Imaging Endpoints in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

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1 TABLE OF CONTENTS

[redacted]

3 INTRODUCTION

Study VX15-661-112 is a phase 2, randomized, placebo-controlled, double-blind study to evaluate the effect of vx-661 in combination with ivacaftor on chest imaging endpoints in subjects aged 12 years and older with cystic fibrosis, homozygous for the *F508del CFTR* mutation.

This statistical analysis plan (SAP) Methods is based on the approved clinical study protocol (CSP), dated 26 February 2018, version 5.0. This SAP addresses the efficacy and safety objective of the study and describes the planned statistical analyses and data presentations for the CSR.

Vertex Biometrics department or a designated Contract Research Organization (CRO) will perform the statistical analysis of the safety and efficacy data. SAS® Version 9.4 Software (SAS Institute, Cary, North Carolina, USA) or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to final database lock.

4 STUDY OBJECTIVES

4.1 Primary Objective(s)

- To evaluate the treatment effect of VX-661 in combination with ivacaftor (VX-661/ivacaftor) on chest imaging endpoints as evaluated using low-dose computed tomography (LDCT) at Week 72 in subjects with CF who are homozygous for the *F508del* mutation on the CF transmembrane conductance regulator (*CFTR*) gene

4.2 Secondary Objectives

- To evaluate the safety of VX-661/ivacaftor through Week 72

[redacted]

[redacted]

5 STUDY ENDPOINTS

5.1 Efficacy Endpoints

- Absolute change in Total Brody/CF-CT score from baseline at Week 72 using LDCT.

5.2 Safety Endpoints

The safety and tolerability is evaluated via the following endpoints:

- Adverse events (AEs)
- Clinical laboratory values (hematology, serum chemistry, coagulation studies, vitamin levels, lipid panel, and urinalysis)
- Standard digital electrocardiograms (ECGs)
- Vital signs
- Pulse Oximetry

[redacted]

6 STUDY DESIGN

6.1 Overall Design

This is a Phase 2, randomized, placebo-controlled, double-blind parallel-group, multicenter study in subjects with CF who are homozygous for the *F508del-CFTR* mutation. This study is designed to evaluate the treatment effect of VX-661/ivacaftor on chest imaging endpoints during 72 weeks of treatment. LDCT [redacted] will be used for chest imaging. The images will be evaluated using the Brody/CF-CT scoring system. Safety over 72 weeks of treatment will also be evaluated.

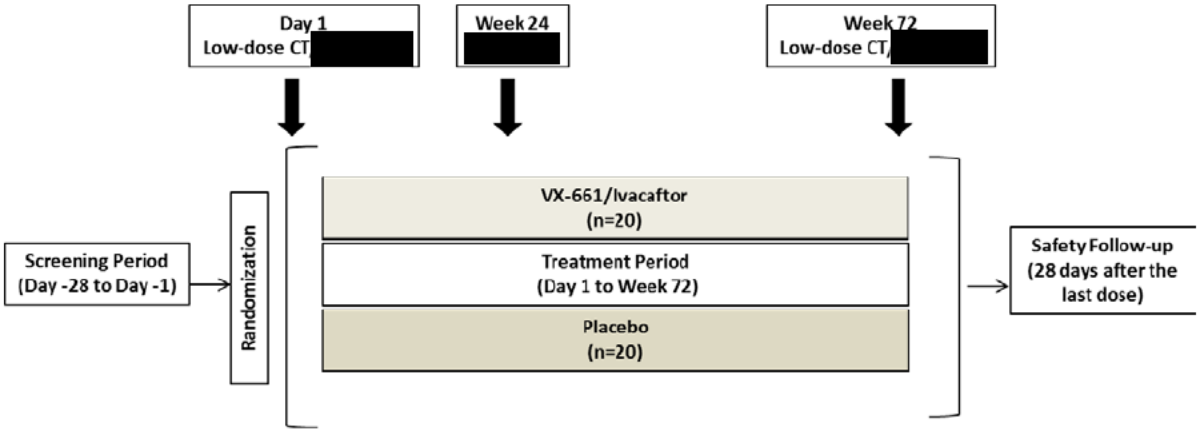
Figure 6-1 shows a schematic of the study design. This study includes a Screening Period, a 72-week Treatment Period, and a Safety Follow-up Visit. Following a 28-day screening period, approximately 40 subjects will be randomized (1:1) to 1 of the 2 treatment arms, active or placebo, on Day 1.

The active treatment regimen will be comprised of a morning dose of a fixed-dose combination (FDC) tablet of VX-661 100-mg/ivacaftor 150-mg and an evening dose of

ivacaftor 150-mg to be taken approximately 12 hours after the morning dose. The placebo regimen will be visually-matched tablets to be taken on the same schedule as the active treatment.

The study will be double-blind. Subjects who complete the study may have the opportunity to receive VX-661/ivacaftor, provided they meet criteria, until VX-661/ivacaftor is commercially available to them or development is terminated. After completing Study VX15-661-112 (Study 112), subjects who meet the criteria may have the opportunity to participate in future Vertex programs with VX-661/ivacaftor, which may include additional scans.

Figure 6-1 VX15-661-112: Study Design



CT: computed tomography;

6.2 Sample Size and Power

The primary endpoint is the absolute change from baseline of Total Brody/CF-CT score measured by the Brody/CF-CT score system at Week 72 using LDCT. The difference between the VX-661/ivacaftor group and the placebo group in the mean change from baseline in Total Brody/CF-CT score at Week 72 will be estimated.

This is an exploratory, Phase 2 study; the sample size is not based on statistical power. With 40 subjects (20 per arm), the study is aimed to explore changes in the Total Brody score over a 72 week period and for VX-661/ivacaftor versus placebo, based on the published literature[1,2].

6.3 Randomization

Approximately 40 subjects who meet the eligibility criteria will be randomized (1:1) to 1 of 2 treatment arms.

An interactive web response system (IWRS) will be used to assign subjects to treatment. The IWRS will use a list of randomization codes generated by a designated vendor .

6.4 Blinding

This is a double-blind study.

Imaging Data Blinding

Despite treatment blinding, knowledge of the LDCT [redacted] results has the potential to suggest whether a subject has been administered active study drug or placebo. Therefore, during the conduct of the study, the Vertex study team will have no access to the postdose imaging data. The vendor for central reading of the imaging data will send only the blinded files (blinded treatment group, with real scores for baseline, but with dummy scores for all the imaging assessments after baseline) to Vertex to be used for developing the statistical programs. Furthermore, subjects and their caregiver should not be informed of their study-related imaging results during the Treatment Period regardless of whether the subject has prematurely discontinued treatment.

CT scans [redacted] will have a clinical over-read by a site radiologist blinded to study drug assignment. Any urgent safety-related findings should be communicated to the Vertex medical monitor, who may recommend follow-up by the site principal investigator. The Vertex medical monitor will facilitate any discussion with the central readers as needed.

[redacted]

7 ANALYSIS SETS

The **All Subjects Set** is defined as all subjects who have been randomized or have received at least 1 dose of study medication. This analysis set will be used in subject listings and disposition summary table, unless otherwise specified.

The **Full Analysis Set** (FAS) is defined as all randomized subjects who have received at least 1 dose of study drug. The FAS is to be used in efficacy analyses in which subjects will be analyzed according to their randomized treatment group.

The **Safety Set** is defined as all subjects who received at least 1 dose of study drug. The Safety Set is to be used for all safety analyses in which subjects will be analyzed according to the treatment they received.

8 STATISTICAL ANALYSIS

8.1 General Considerations

The Schedule of Assessments is provided in Appendix A (Section 10.1).

All individual subject data for those randomized or exposed to study drug will be presented in data listings.

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

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

Absolute Change from baseline will be calculated as Postbaseline value - Baseline value.

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

Treatment Emergent (TE) Period will include the time from the first dose to Safety Follow-up Visit. For subjects who do not have a Safety Follow-up Visit because they rolled over into the open-label extension study within 28 days after the last dose of study drug, the end of the TE period will be the date of rollover into the extension study. For subjects who do not have a Safety Follow-up Visit and did not roll over into the extension study, the end of the the TE period will be 28 days after the date of last dose. The TE period will be used for safety analyses unless otherwise specified.

Unscheduled Visits: Unscheduled visit measurements 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/minimum on-treatment values and maximum/minimum changes from baseline values for safety analyses;
- In individual subject data listings where appropriate.

Visit Windowing Rules: The analysis visit windows for protocol-defined visits are provided in Appendix B (Section 10.2). 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,

- 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.
- Assessments at early treatment termination (ETT) visit will follow the windowing rules for regular visits up to Week 72.
- Assessments at safety follow-up (SFU) visit will follow the windowing rules for regular visits if it falls within the upper boundary of the window for Week 72, or remain as SFU if it goes beyond the upper boundary of the window for Week 72.

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; 2) if there are multiple records within the same distance from the target day, the latest record will be used; or 3) SFU visit will not be windowed, instead, used per nominal visit in relevant analyses.

[redacted]

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

8.2.1 Subject Disposition

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

- All Subjects Set (randomized or dosed)
- Randomized
- Randomized but not dosed
- Full Analysis Set (FAS)
- Safety Set

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

- Completed study drug treatment
- Treatment ongoing
- Prematurely discontinued treatment and the reason for discontinuations
- Completed study
- Prematurely discontinued the study and the reasons for discontinuations

8.2.2 Subject Demographics and Baseline Characteristics

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

Demographic data will include the following:

- Sex (female and male)
- Age
- Age group at screening (<18, and ≥18 years)
- 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)

[redacted]

Disease characteristics will include the following:

- Percent predicted FEV_1 at baseline
- Sweat Chloride at screening
- Use of dornase alfa
- Use of inhaled antibiotic
- Use of bronchodilator
- Use of inhaled bronchodilator
- Use of inhaled hypertonic saline
- Use of inhaled corticosteroids
- Colonization of *Pseudomonas aeruginosa* (Positive, Negative)

[redacted]

- Brody/CF-CT total score at baseline

[redacted]

8.2.3 Prior and Concomitant Medications

Medications taken during this study will be coded using the World Health Organization Drug Dictionary Enhanced (WHO-DDE) and categorized as the following:

- **Prior medication:** any medication that started before the first dose of study drug, regardless of when the medication ended.
- **Concomitant medication:** medication continued or newly received at or after the first dose of study drug through the end of TE period.

- **Post-treatment medication:** medication continued or newly received after the TE period.

A given medication can be classified as a prior, a concomitant, 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 and it cannot be determined whether it was taken before the first dose, concomitantly, or beyond the TE period, it will be considered as prior, concomitant, and post-treatment.

For the FAS, prior medications and concomitant medications will be summarized descriptively by: 1) preferred name; and 2) anatomic class (ATC) level 1, ATC level 2, and preferred name. Frequent (≥5% in any treatment group) prior medications and concomitant medications will be summarized descriptively by preferred name. Post-treatment medications will be listed by subject.

Details for imputing missing or partial start and/or stop dates of medication are described in Appendix C (Section 10.3).

8.2.4 Study Drug Exposure

Exposure summaries will be based on the Safety Set.

Duration of study drug exposure is defined as: last dose date – first dose date + 1 day, regardless of any interruption in dosing between the first and the last dose. For the purposes of DMC, if the date from End of Dosing CRF page is not available, the end of treatment date will be assumed to be the date of datacut.

Duration of study drug exposure, as well as number of tablets administered defined as (Total number of tablets dispensed) - (Total number of tablets returned), will be summarized descriptively (number, mean, SD, SE, median, minimum, and maximum). Additionally, the total duration of study drug exposure, defined as the sum of the subject's duration of treatment exposure and expressed in patient years, will be provided.

If the last dose date of study drug is missing, the latest of the date of subject's treatment discontinuation or the date of treatment completion will be used for analysis purposes.

8.2.5 Study Drug Compliance

Study drug compliance will be measured by the compliance rate; summarized based on the Safety Set and presented by treatment group.

Compliance rate will be calculated as follows:

$$100 \times [1 - (\text{Total number of days study drug interrupted}) / (\text{Duration of study drug exposure})].$$

The total number of days study drug interrupted is defined as the total of number of days the study drug was interrupted in each interruption interval; where number of days study drug interrupted in each interval is defined as the interruption end date - the corresponding interruption start date + 1.

The Compliance rate will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max and into the categories of <80% or ≥80%.

A list of subjects with <80% compliance rate will be provided.

8.2.6 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, but the blinded team should categorize them as IPDs only if they have the potential to affect interpretation of study results.

IPDs (from the clinical database or from the site deviation log) will be summarized descriptively based on the FAS and presented by treatment group. Additionally, IPDs will be provided as a subject data listing.

8.3 Efficacy Analysis

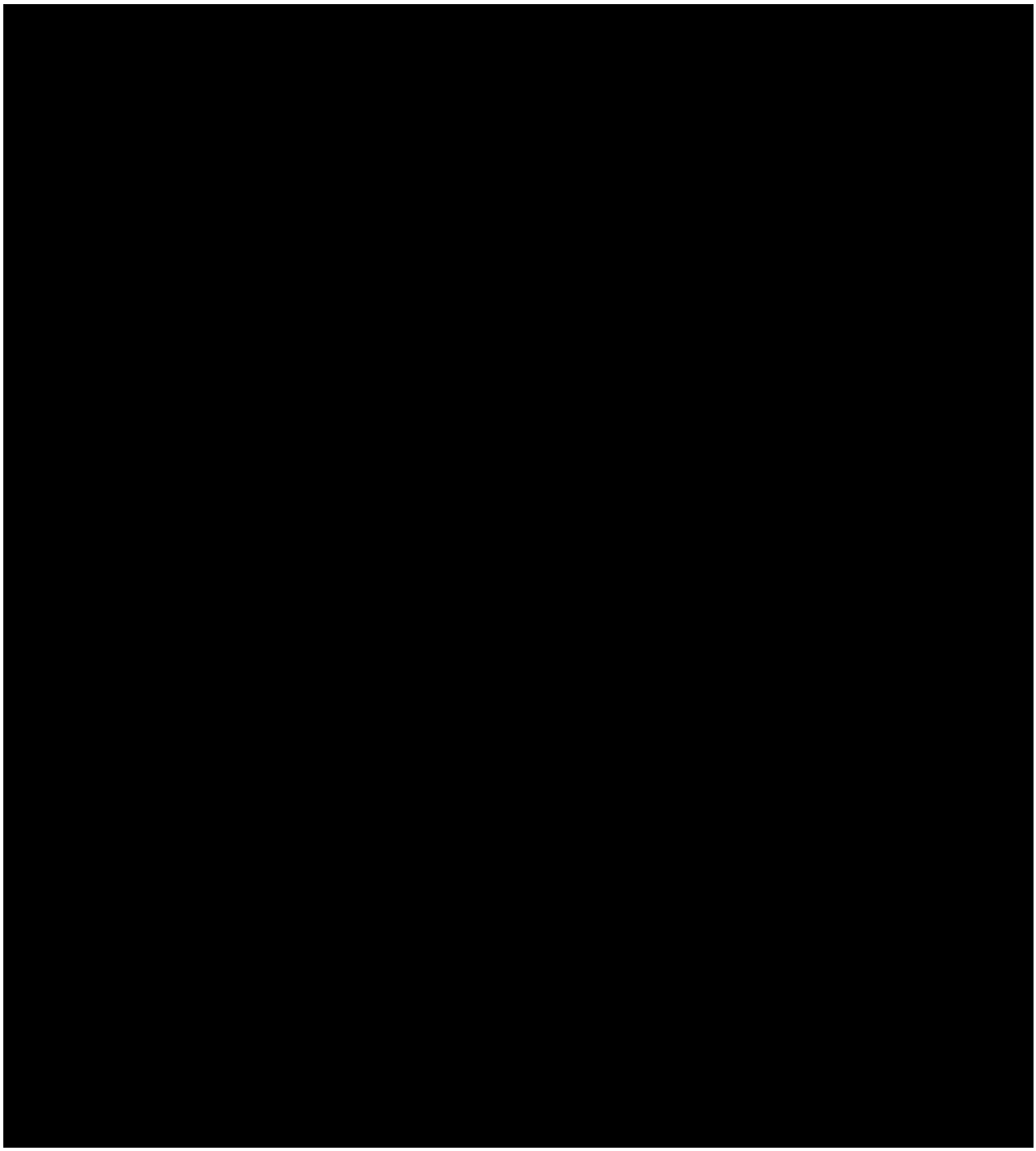
Assessment of efficacy of VX-661/ivacaftor is the primary objective of this study.

8.3.1 Analysis of Primary Efficacy Endpoint

The primary endpoint is the absolute change from baseline of Total Brody/CF-CT score at Week 72 using LDCT. The primary analysis will be based on an analysis of covariance (ANCOVA) model with the change from baseline of Total Brody/CF-CT score at Week 72 as dependent variable, treatment, sex (male versus female), and age (12-17 years vs. 18 years and older) as covariates. LDCT images will be scored by 2 central reader(s) blinded to treatment group and visit time point. The difference between the VX-661/ivacaftor group and the placebo group in mean change from baseline in Total Brody/CF-CT score at Week 72 will be estimated using the FAS.

The primary result obtained from the model will be the estimated treatment effect in each treatment group (with a 95% confidence interval), the estimated between-group difference in treatment effects, and a 95% confidence interval (CI) for the difference. For missing data, no imputation will be performed.

Summary statistics (n, mean, SD, SE, median, minimum, and maximum) will be presented by treatment group at each scheduled visit and for absolute change from baseline at each scheduled visit.



8.4 Safety Analysis

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

- Adverse events
- Clinical laboratory values (hematology, serum chemistry, coagulation studies, vitamin levels, lipid panel, and urinalysis)
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry

Safety endpoints will be analyzed based on the Safety Set (for each applicable treatment period). Only descriptive analysis of safety will be performed and no statistical testing will be performed.

8.4.1 Adverse Events

For analysis purpose, AEs will be categorized as pretreatment AEs, treatment-emergent adverse events (TEAEs), or post-treatment AEs:

Pretreatment AE: any AE that started before the first dose of study drug.

TEAE: any AE that increased in severity or that was newly developed at or after the first dose of study drug through the end of TE period.

Post-treatment AE: any AE that increased in severity or that was newly developed after the TE period.

For AEs with missing or partial start dates, AE start dates will be imputed according to the rules in Appendix G (Section 10.7).

An adverse event overview table will be provided with the following for TE period:

- Number of TEAEs (total number of TEAEs only)
- Subjects with any TEAEs
- Subjects with TEAEs by relationship
- Subjects with TEAEs by maximum severity
- Subjects with TEAEs leading to treatment discontinuation
- Subjects with TEAEs leading to treatment interruption
- Subjects with grade 3/4 TEAEs
- Subjects with related TEAEs
- Subjects with serious TEAEs
- Subjects with related serious TEAEs
- Subjects with TEAE leading to death

The following summary tables of TEAEs will be presented by treatment group:

- All TEAEs
- Grade 3/4 TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Related TEAEs
- Serious TEAEs
- Related serious TEAEs
- TEAEs leading to death

When summarizing the number and percentages of subjects, subjects with multiple occurrences of the same adverse event or a continuing adverse event will be counted once, and only the maximum severity level will be presented in the severity summaries, and the worst/highest relationship level in the relationship summaries.

The following summary tables will be presented by treatment showing number and percentage of subjects

- TEAEs and SAEs by SOC and PT
- TEAEs and SAEs by PT
- TEAEs and SAEs by SOC and PT and Severity

- TEAEs and SAEs by SOC and PT and Relationship

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

8.4.2 Clinical Laboratory

For the treatment emergent laboratory measurements, the raw values and change from baseline values of the continuous hematology and chemistry results will be summarized in SI units by treatment group at each scheduled time point. For hematology and chemistry, the number and percentage of subjects with abnormal low (<LLN) value and with abnormal high (>ULN) value at each scheduled time point will be summarized.

For LFT and CPK results (alanine aminotransferase [ALT], aspartate aminotransferase [AST], serum alkaline phosphatase [ALP], total bilirubin and CPK), the following additional analyses will be conducted:

- The number and percentage of subjects who meet the thresholds for LFT and CPK according to the criteria defined in Appendix H (Section 10.8) will be summarized by visit and during the TE period. The shift of the threshold criteria from baseline to post baseline will be summarized.
- For each LFT, the box plot of LFT value/ULN will be provided against visit.
- A scatter plot of maximum values of ALT versus maximum values of total bilirubin will also be presented. Note that the ALT and Total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3xULN for ALT and a horizontal line corresponding to 2xULN for total bilirubin. A similar graph of maximum values of AST versus maximum values of total bilirubin will be presented as well.
- 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 visits will be included.

Results of GI/Nutrition laboratory parameters (specified in SAP M2) will be summarized and subject data listings will be provided. The number and percentage of subjects with abnormal low (<LLN) value and with abnormal high (>ULN) value at each scheduled time point will be summarized for GI/nutritional parameter and listed separately. In addition, boxplots by visit will be provided for GI/Nutrition laboratory parameters.

Results of serum pregnancy test, 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, and coagulation values outside the reference ranges will be provided. These listings will include data from scheduled and unscheduled time points.

8.4.3 Standard 12-Lead Electrocardiogram

For the 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, QT, and QTc for HR intervals (QTcF), QRS duration, and HR.

The number and percentage of subjects with ECG event meeting threshold criteria during the treatment-emergent period will be summarized by treatment, ECG parameters, and visit. The threshold criteria are provided in Appendix H (Section 10.8).

8.4.4 Vital Signs

For the treatment emergent vital signs measurements, the raw values and change from baseline values will be summarized by treatment group at each scheduled time point: 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 with vital signs meeting threshold during the treatment-emergent period will be summarized by treatment, vital signs parameters, and visit. The threshold criteria are provided in Appendix H (Section 10.8).

8.4.5 Pulse Oximetry

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

8.4.6 Physical Examination

PE findings will be presented as a data listing only.

9 INTERIM AND DMC ANALYSES

9.1 Interim Analysis

No formal interim analysis is planned.

9.2 DMC Analysis

An independent data monitoring committee (IDMC) will be formed before study initiation. The IDMC's objectives and operational details will be defined in a separate document (IDMC Charter) which will be finalized before the first subject is screened in the study. The IDMC will conduct regular planned safety reviews of study data as outlined in the IDMC Charter.

Analyses for IDMC purposes are described in a separate IDMC SAP.

10 LIST OF APPENDICES

10.1 Appendix A: Schedule of Assessments

Table 10-1 Study VX15-661-112: Screening

Event/Assessment	Screening Period (Day -28 through Day -1)
Informed consent (and assent, when applicable)	X
Demographics	X
Medical history	X
Ophthalmological history	X
CF genotype[a]	X
FSH[b]	X
Serum pregnancy test (all females of childbearing potential)[c]	X
Hematology	X
Coagulation	X
Serum chemistry	X
Urinalysis	X
Weight and height[d]	X
Ophthalmologic examination[e]	X
Complete physical examination	X
Vital signs[f]	X
Pulse oximetry[f]	X
Standard 12-lead ECG[g]	X
Spirometry[h]	X
Inclusion/exclusion criteria review	X
Prior and concomitant medications	X
Sweat chloride[i]	X
AEs and SAEs	Continuous from signing of the ICF and assent (where applicable) through the Safety Follow-up Visit

AE: adverse event; CF: cystic fibrosis; ECG: electrocardiogram; FSH: follicle-stimulating hormone; ICF: informed consent form; SAE: serious adverse event.

[a] All subjects will be tested for CF genotype. Specific instructions will be provided in the Laboratory Manual. CF genotyping may be waived if the subject has a documented result from a previous Vertex study.

[b] FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be ≥40 mIU/mL to be considered postmenopausal.

[c] Any female subject who does not meet the criteria for non-childbearing potential is considered to be of childbearing potential and must have a serum pregnancy test.

[d] Weight and height will be measured with shoes off.

[e] An ophthalmologic examination will be conducted on subjects of all ages by an ophthalmologist. The ophthalmologic examination does not need to be repeated if there is documentation of an examination that met the protocol criteria and was conducted within 3 months before the start of the Screening Period or if there is documentation of bilateral lens removal (Section 11.6.8 of Clinical Study Protocol).

[f] Vital signs and pulse oximetry will be collected after the subject has been at rest (seated or supine) for 5 minutes.

[g] A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes.

[h] Spirometry may be performed pre- or postbronchodilator (Section 11.5.2).

[i] A sweat chloride test must be performed at the Screening Visit if an eligible sweat chloride value is not available in the subject's medical records and the Screening Visit value is needed to establish eligibility. For subjects using sweat chloride values documented in their medical records to establish eligibility, the sweat chloride test at the Screening Visit is optional.

Table 10-2 Study VX15-661-112: Treatment Period (Day 1 to Week 72), Early Termination of Treatment Visit, and Safety Follow-up Visit Assessments

Event/Assessment[a]	Day 1	Day 15 (± 3 days)	Week 4, Week 12, (± 1 week)	Week 24 (± 1 week)	Week 36, Week 48, Week 60 (± 1 week)	Week 72 (± 1 week)	Early Termination of Treatment Visit (Within 7 days After Last Dose of Study Drug)	Safety Follow-up Visit 4 weeks (± 7 days) After Last Dose of Study Drug[b]
Clinic visit	X	X	X	X	X	X	X	X
Inclusion and exclusion criteria review[c]	X							
Randomization[d]	X							
[redacted]								
Complete physical examination[f]	X					X	X	X
Pregnancy test[g]	urine		urine	urine	urine	urine	serum	serum

[a] All assessments will be performed before dosing unless noted otherwise. If study drug is not administered on the day of the visit (i.e., study drug interruption or premature discontinuation of study drug treatment), only 1 set of assessments will be collected.

[b] The Safety Follow-up Visit is not required for subjects who complete the Week 72 Visit and have enrolled in the TEZ/IVA open-label extension study, VX14-661-110, within 28 days after the last dose of study drug.

[c] The screening inclusion and exclusion criteria should be re-reviewed before administration of study drug on Day 1.

[d] Randomization must occur after the informed consent/assent has been obtained and all inclusion and exclusion criteria are met and before the first dose of study drug. Randomization will be done through an interactive web response system. Randomization may occur on Day −1 if the above conditions for randomization have been met.

[redacted]

In addition to the indicated visits, a symptom-targeted physical examinations will occur at any time during the study if triggered by adverse events (AEs) or if deemed necessary by the investigator.

[g] Pregnancy tests will be performed for all female subjects of childbearing potential. Day 1 results will be reviewed before dosing and the Low-dose CT scan. Week 72 results will be reviewed before the Low-dose CT scan.

Table 10-2 Study VX15-661-112: Treatment Period (Day 1 to Week 72), Early Termination of Treatment Visit, and Safety Follow-up Visit Assessments

Event/Assessment[a]	Day 1	Day 15 (± 3 days)	Week 4, Week 12, (± 1 week)	Week 24 (± 1 week)	Week 36, Week 48, Week 60 (± 1 week)	Week 72 (± 1 week)	Early Termination of Treatment Visit (Within 7 days After Last Dose of Study Drug)	Safety Follow-up Visit 4 weeks (± 7 days) After Last Dose of Study Drug[b]
[redacted]								
Low-dose CT scan[h]	X					X		
[redacted]								
Standard digital ECG[m]	X	X	X	X	X	X	X	X
Vital signs[n]	X	X	X	X	X	X	X	X
Pulse oximetry[n]	X	X	X	X	X	X	X	X
[redacted]								

[h] Low-dose CT scans [redacted] should be performed on the same day. If not possible for logistical reasons, Low-dose CT scans [redacted] should be performed within ± 4 days of the scheduled visit. Day 1 assessments must be completed before dosing. The Week 72 CT scan may be delayed for up to 60 days if the subject is recovering from a pulmonary exacerbation. The medical monitor should be notified about the extension. The scan should be done after the pulmonary exacerbation is resolved and at least 28 days after the antibiotic regimen for the treatment of pulmonary infection has been completed. If this antibiotic regimen is not completed by the end of the 60-day extension, the subject may complete the CT scan within the first 30 days of enrolling in Study VX14-661-110; or within 1 week of [redacted]

[m] All standard 12-lead ECGs will be performed before dosing and after the subject has been supine for at least 5 minutes. The predose ECGs collected at the Day 1 Visit will be performed in triplicate.

[n] Vital signs and pulse oximetry will be collected before dosing and after the subject has been at rest (seated or supine) for at least 5 minutes. In addition to the indicated visits, symptom-targeted vital signs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

[redacted]

Table 10-2 Study VX15-661-112: Treatment Period (Day 1 to Week 72), Early Termination of Treatment Visit, and Safety Follow-up Visit Assessments

Event/Assessment[a]	Day 1	Day 15 (± 3 days)	Week 4, Week 12, (± 1 week)	Week 24 (± 1 week)	Week 36, Week 48, Week 60 (± 1 week)	Week 72 (± 1 week)	Early Termination of Treatment Visit (Within 7 days After Last Dose of Study Drug)	Safety Follow-up Visit 4 weeks (± 7 days) After Last Dose of Study Drug[b]
Hematology	X			X	Wk 48 only	X	X	X
Lipid and vitamin levels	X			X	Wk 48 only	X	X	X
Coagulation	X					X		X
Serum chemistry[p]	X	X	X	LFT only	LFT only	X	X	X
Urinalysis	X					X		X
Study drug count		X	X	X	X	X		
Meal(s) or snack(s) at site[q]	X	X	X	X	X			

[redacted] CT: computed tomography; ECG: electrocardiogram; LFT: liver function test; [redacted]

[p] Blood samples will be collected before the dose of study drug. At Weeks 24, 36, 48, and 60, only samples for LFT analysis will be collected.
[q] Food will be provided after all predose assessments have occurred.

Table 10-2 Study VX15-661-112: Treatment Period (Day 1 to Week 72), Early Termination of Treatment Visit, and Safety Follow-up Visit Assessments

Event/Assessment[a]	Day 1	Day 15 (± 3 days)	Week 4, Week 12, (± 1 week)	Week 24 (± 1 week)	Week 36, Week 48, Week 60 (± 1 week)	Week 72 (± 1 week)	Early Termination of Treatment Visit (Within 7 days After Last Dose of Study Drug)	Safety Follow-up Visit 4 weeks (± 7 days) After Last Dose of Study Drug[b]
Study drug dosing[r]	Day 1 through Week 72							
Ophthalmologic examination						X[s]	X[t]	X[t]
Concomitant medications	X	X	X	X	X	X	X	X
Concomitant treatments and procedures	X	X	X	X	X	X	X	X
Adverse events and serious adverse events	Continuous from signing of the informed consent form and assent (where applicable) through the Safety Follow-up Visit							

[r] Subjects will take study drug as specified in Section 10.2. On days of scheduled visits, the subject's dose of study drug will be administered at the site after predose assessments have been completed. Study drug administration should be completed within 5 minutes. At the Week 72 Visit, the morning dose of study drug will NOT be administered. The last dose of study drug will be the evening dose administered the day before the Week 72 Visit. If the Week 72 CT scan is delayed to allow a subject to recover from [redacted], study drug will continue for up to 60 days until the Week 72 CT scan has been completed or the subject has enrolled in Study VX14-661-110; for these subjects, the last dose of study drug will be the evening dose administered the day before the CT scan or before the Day 1 Visit of Study VX14-661-110.

[s] All subjects <18 years of age at the Screening Visit will have an ophthalmologic examination conducted by a licensed ophthalmologist at Week 72. This exam may be completed within 4 weeks before the Week 72 Visit, but must be completed by the end of the Week 72 Visit.

[t] Subjects <18 years of age at the Screening Visit who discontinue treatment after receiving at least 1 dose of study drug will have an ophthalmologic examination performed by a licensed ophthalmologist at the Safety Follow-up or the Early Termination of Treatment Visit. This examination may be completed at either the Early Termination of Treatment or Safety Follow-up Visit, but must be completed by the end of the Safety Follow-up Visit.

10.2 Appendix B: Analysis Visit Window Mapping Rules for Efficacy and Safety Measurements

Table 10-3 Visit Window Mapping Rules

Assessments	Visit	Target Study Day	Visit Window (in study days)
Standard 12-lead ECG Vital signs Pulse oximetry Serum Chemistry	Baseline	1	≤1
	Day 15	15	[2, 22]
	Week 4	29	[23, 57]
	Week 12	85	[58, 127]
	Week 24	169	[128, 211]
	Week 36	253	[212, 295]
	Week 48	337	[296, 379]
	Week 60	421	[380, 463]
	Week 72	505	[464, 519]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up Visit	N/A	Nominal
Hematology Lipid and Vitamin Levels	Baseline	1	≤1
	Week 24	169	[2, 253]
	Week 48	337	[254, 421]
	Week 72	505	[422, 519]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up Visit	N/A	Nominal
[redacted]			
Coagulation	Baseline	1	≤1
	Week 72	505	[464, 519]
	Safety Follow-up Visit	N/A	Nominal

10.3 Appendix C: Imputation Rules for Missing Prior/Concomitant Medication Dates

As an intermediate step for programming purposes, medications with missing or partially missing start dates will use 2000 to impute a missing year, January for a missing month, and 1 for a missing day. Medications with missing or partially missing stop dates will use 2050 to impute for a missing year, December for a missing month, and the last day of the month for a missing day. The logic to decide the category of a medication is presented in Table 10-4:

Table 10-4 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

10.4 Appendix D: Coefficients for Hankinson and Wang Methods for Calculating Predicted Spirometry Parameters

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 (L) will be calculated using the Hankinson[2] and Wang[3] standards.

The Hankinson standard will be applied to male subjects 18 years and older and female subjects 16 years and older; the Wang standard will be applied to male subjects 6 to 17 years and female subjects 6 to 15 years of age. During the study, the subjects who have a birthday that would move them from Wang to Hankinson will use the Wang standard before that birthday and the Hankinson standard at or after that birthday.

Hankinson Normal Values (HNVs) will be calculated for FEV_1, forced vital capacity (FVC), forced expiratory flow mid expiratory phase ($FEF_{25-75\%}$), and FEV_1/FVC% using the Hankinson equation:

$$\text{Predicted lung function parameter} = b0+b1 \times age+b2 \times age^2+ b3 \times height^2$$

In the equation, height is given in centimeters, age is given in years, and the coefficients b_0, b_1, b_2, and b_3 are determined based on subject's sex, race, and age group as shown in Table 10-5.

Wang Normal Values (WNVs) will be calculated for FEV_1, FVC, $FEF_{25-75\%}$, and FEV_1/FVC using the Wang equation:

$$\ln(\text{Predicted lung function parameter}) = \alpha + \beta \ln(\text{height})$$

Wang Normal Values (WNVs) will be calculated for FEV_1, FVC, $FEF_{25-75\%}$, and FEV_1/FVC using the Wang equation. In the equation, height is given in meters, and the coefficients α and β are determined based on subject's sex, race, and age as shown in Table 10-6 and Table 10-7.

[redacted]

Table 10-5 HNVs Equation Coefficients by Sex, Race, and Age

Parameter	Sex	Race	Age (years)	b_0	b_1	b_2	b_3
HNV_{FEV1}	Male	Caucasian	<20	-0.7453	-0.04106	0.004477	0.00014098
			≥20	0.5536	-0.01303	-0.000172	0.00014098
		African American	<20	-0.7048	-0.05711	0.004316	0.00013194
			≥20	0.3411	-0.02309		0.00013194
		Mexican American	<20	-0.8218	-0.04248	0.004291	0.00015104
			≥20	0.6306	-0.02928		0.00015104
	Female	Caucasian	<18	-0.8710	0.06537		0.00011496
			≥18	0.4333	-0.00361	-0.000194	0.00011496
		African American	<18	-0.9630	0.05799		0.00010846
			≥18	0.3433	-0.01283	-0.000097	0.00010846
		Mexican American	<18	-0.9641	0.06490		0.00012154
			≥18	0.4529	-0.01178	-0.000113	0.00012154
HNV_{FVC}	Male	Caucasian	<20	-0.2584	-0.20415	0.010133	0.00018642
			≥20	-0.1933	0.00064	-0.000269	0.00018642
		African American	<20	-0.4971	-0.15497	0.007701	0.00016643
			≥20	-0.1517	-0.01821		0.00016643
		Mexican American	<20	-0.7571	-0.09520	0.006619	0.00017823
			≥20	0.2376	-0.00891	-0.000182	0.00017823
	Female	Caucasian	<18	-1.2082	0.05916		0.00014815
			≥18	-0.3560	0.01870	-0.000382	0.00014815
		African American	<18	-0.6166	-0.04687	0.003602	0.00013606
			≥18	-0.3039	0.00536	-0.000265	0.00013606
		Mexican American	<18	-1.2507	0.07501		0.00014246
			≥18	0.1210	0.00307	-0.000237	0.00014246
$HNV_{FEF25-75\%}$	Male	Caucasian	<20	-1.0863	0.13939		0.00010345
			≥20	2.7006	-0.04995		0.00010345
		African American	<20	-1.1627	0.12314		0.00010461
			≥20	2.1477	-0.04238		0.00010461
		Mexican American	<20	-1.3592	0.10529		0.00014473
			≥20	1.7503	-0.05018		0.00014473
	Female	Caucasian	<18	-2.5284	0.52490	-0.015309	0.00006982
			≥18	2.3670	-0.01904	-0.000200	0.00006982
		African American	<18	-2.5379	0.43755	-0.012154	0.00008572
			≥18	2.0828	-0.03793		0.00008572
		Mexican American	<18	-2.1825	0.42451	-0.012415	0.00009610
			≥18	1.7456	-0.01195	-0.000291	0.00009610
$HNV_{FEV1/FVC\%}$	Male	Caucasian		88.066	-0.2066		
		African American		89.239	-0.1828		
		Mexican American		90.024	-0.2186		
	Female	Caucasian		90.809	-0.2125		
		African American		91.655	-0.2039		
		Mexican American		92.360	-0.2248		

Source: Reference (Hankinson JL, 1999) (Tables 4, 5 and 6)

Table 10-6 WNVs Equation Coefficients by Sex and Age in White Boys and Girls

		FEV_1		FVC		$FEF_{25-75\%}$		FEV_1/FVC	
Sex	**Age**	**α**	**β**	**α**	**β**	**α**	**β**	**α**	**β**
Male	6	-0.109	2.252	-0.024	2.470			-0.078	-0.248
	7	-0.104	2.270	-0.018	2.489			-0.086	-0.220
	8	-0.089	2.257	0.005	2.443	0.264	1.505	-0.091	-0.199
	9	-0.063	2.197	0.017	2.426	0.308	1.443	-0.086	-0.206
	10	-0.057	2.212	0.030	2.407	0.290	1.557	-0.081	-0.209
	11	-0.093	2.324	0.009	2.468	0.242	1.738	-0.101	-0.147
	12	-0.161	2.512	-0.061	2.649	0.165	1.982	-0.101	-0.133
	13	-0.292	2.843	-0.175	2.924	0.007	2.396	-0.116	-0.085
	14	-0.329	2.983	-0.219	3.060	0.014	2.483	-0.106	-0.087
	15	-0.141	2.709	-0.079	2.859	0.241	2.163	-0.060	-0.155
	16	0.062	2.409	0.104	2.591	0.503	1.764	-0.045	-0.178
	17	0.262	2.099	0.253	2.374	0.762	1.368	0.008	-0.272
Female	6	-0.109	1.949	-0.013	2.007			-0.097	-0.055
	7	-0.144	2.243	-0.062	2.385			-0.084	-0.132
	8	-0.137	2.239	-0.055	2.381	0.247	1.668	-0.079	-0.152
	9	-0.123	2.222	-0.039	2.351	0.254	1.710	-0.084	-0.128
	10	-0.161	2.364	-0.068	2.458	0.195	1.933	-0.092	-0.097
	11	-0.223	2.558	-0.120	2.617	0.161	2.091	-0.102	-0.061
	12	-0.264	2.709	-0.174	2.776	0.185	2.120	-0.090	-0.067
	13	-0.153	2.535	-0.061	2.576	0.294	1.976	-0.093	-0.040
	14	0.046	2.178	0.139	2.208	0.450	1.711	-0.096	-0.026
	15	0.148	2.008	0.210	2.099	0.581	1.486	-0.062	-0.093

Source: Reference (Wang X, 1993) (Tables 2 and 3)

Table 10-7 WNVs Equation Coefficients by Sex and Age in Black Boys and Girls

		FEV_1		FVC		$FEF_{25-75\%}$		FEV_1/FVC	
Sex	**Age**	**α**	**β**	**α**	**β**	**α**	**β**	**α**	**β**
Male	6	-0.166	1.723	-0.088	1.961			-0.091	-0.152
	7	-0.122	1.846	-0.040	2.040			-0.091	-0.153
	8	-0.225	2.271	-0.094	2.323	0.097	1.544	-0.118	-0.104
	9	-0.142	2.059	-0.074	2.308	0.255	1.248	-0.079	-0.218
	10	-0.157	2.117	-0.110	2.417	0.230	1.428	-0.047	-0.303
	11	-0.176	2.166	-0.138	2.453	0.256	1.438	-0.048	-0.263
	12	-0.307	2.548	-0.224	2.710	0.085	1.936	-0.084	-0.162
	13	-0.486	2.962	-0.342	2.975	-0.121	2.476	-0.141	-0.018
	14	-0.472	3.010	-0.337	3.035	-0.115	2.536	-0.123	-0.050
	15	-0.318	2.789	-0.226	2.889	0.170	2.120	-0.070	-0.140
	16	0.074	2.140	0.058	2.425	0.663	1.299	0.018	-0.289
	17	0.053	2.223	0.148	2.310	0.505	1.618	-0.095	-0.087
Female	6	-0.288	2.182	-0.172	2.117			-0.109	0.059
	7	-0.250	2.158	-0.135	2.132			-0.104	-0.030
	8	-0.276	2.295	-0.176	2.362	-0.283	2.990	-0.103	-0.066
	9	-0.294	2.330	-0.200	2.452	0.025	2.062	-0.097	-0.104
	10	-0.344	2.507	-0.230	2.571	0.051	2.028	-0.120	-0.043
	11	-0.308	2.460	-0.204	2.526	0.078	2.006	-0.089	-0.105
	12	-0.219	2.312	-0.107	2.342	0.225	1.804	-0.115	-0.021
	13	-0.117	2.196	-0.042	2.294	0.418	1.504	-0.051	-0.148
	14	0.041	1.920	0.105	2.021	0.574	1.257	-0.063	-0.103
	15	0.203	1.662	0.253	1.787	0.599	1.281	-0.043	-0.139

Source: Reference (Wang X, 1993) (Tables 4 and 5)

10.7 Appendix G: Imputation Rules for Missing AE Start Dates

For missing or partial AE start date, use the imputation rules 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 prior to 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 pre-treatment 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 prior to 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 pre-treatment 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 prior to the first dose date then the AE should be considered as a pre-treatment AE. Otherwise, the AE will be considered as TEAE.

10.8 Appendix H: Threshold Analysis Criteria

Table 10-8 Threshold Criteria for Laboratory Tests

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	<LLN - ≥ 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
Bicarbonate	<LLN >ULN	No CTCAE
Inorganic phosphate	Hypophosphatemia <LLN - ≥ 0.8 mmol/L <0.8 – ≥ 0.6mmol/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	FDA DILI Guidance and CTCAE

	>8 – ≤ 20.0 xULN >20.0 x ULN	
ALT or AST	ALT>3xULN or AST>3xULN	FDA DILI Guidance
Alkaline Phosphatase	>ULN - ≤ 1.5xULN >1.5 – ≤ 2.5 xULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	FDA DILI Guidance 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

Table 10-9 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

Table 10-10 Threshold Criteria for ECGs

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	

Table 10-11 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

11 REFERENCES

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