VERTEX

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan Methods

Protocol Number VX16-661-114, Version 1.0

A Phase 3b, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Safety, Efficacy, and Tolerability of Tezacaftor/Ivacaftor (TEZ/IVA) in an Orkambi-experienced Population Who Are Homozygous for the *F508del-CFTR* Mutation

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2 INTRODUCTION

This SAP, which describes the planned final analyses for Study VX16-661-114, is based on the following:

- The approved clinical study protocol (Version 3.1 for USA and Version 3.2 for the EU, dated on 09 June, 2017),
- The approved electronic case report forms (eCRF) (Version 1.5, dated 16 on March, 2017).

Study VX16-661-114 is a Phase 3b, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Safety, Efficacy, and Tolerability of Tezacaftor/Ivacaftor (TEZ/IVA) in an Orkambi-experienced Population Who Are Homozygous for the *F508del-CFTR* Mutation.

This SAP (Methods) documents the planned final statistical analyses of efficacy and safety endpoints defined in the VX16-661-114 study protocol.

The Vertex Biometrics Department or a designated CRO will perform the statistical analysis of the efficacy and safety data; 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 final clinical data lock and treatment unblinding for the study. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to evaluate the respiratory safety of Tezacaftor in combination with ivacaftor (TEZ/IVA) in subjects with CF homozygous for *F508del* and who discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment

3.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the efficacy of TEZ/IVA in subjects with CF homozygous for *F508del* and who discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment.
- To evaluate patient-reported outcomes after treatment with TEZ/IVA in subjects with CF homozygous for *F508del* who discontinued with Orkambi due to respiratory symptoms considered related to treatment.

4 STUDY ENDPOINTS

4.1 Safety Endpoints (Primary Endpoint)

4.1.1 Primary Safety Endpoint

The primary endpoint is the incidence of respiratory adverse events (AEs) including but not limited to the following categories while patients are on treatment:

- Chest discomfort
- Dyspnea (shortness of breath)
- Respiration abnormal (chest tightness)
- Asthma
- Bronchial hyperreactivity
- Bronchospasm
- Wheezing

4.1.2 Secondary Safety Endpoints

The additional safety endpoints are as follows:

- Incidence of treatment-emergent AEs, SAEs, and discontinuations due to AEs
- Clinical laboratory values
- Physical Examinations
- Vital signs
- Pulse oximetry
- Postdose spirometry on Day 1

4.2 Efficacy Endpoints (Secondary Endpoints)

4.2.1 Key Secondary Efficacy Endpoint

The key efficacy endpoint is the absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline to the average of the Day 28 and Day 56 measurements.

4.2.2 Secondary Efficacy Endpoints

- Relative change in $ppFEV_1$ from baseline to the average of the Day 28 and Day 56 measurements.

- Absolute change in Cystic Fibrosis Questionnaire Revised (CFQ-R) respiratory domain score from baseline to the average of the Day 28 and Day 56 measurements

4.2.3 Additional Secondary Endpoint

- Discontinuation rate through Day 56

5 STUDY DESIGN

5.1 Overview of Study Design

This study includes the following:

- Screening Period (Day −28 through Day −1)
- Treatment Period (Day 1 through Day 56 ± 5 days)
- Safety Follow-up Contact (28 days ± 7 days after the last dose of study drug) for subjects who do not enroll in the long-term, open-label safety study of TEZ/IVA. (Open-label study is an option in the EU only.)

Subjects will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), sex (male versus female), and ppFEV$_1$ severity determined during the Screening Visit (<40% versus ≥40% predicted), and then randomized (1:1) to 1 of the following 2 treatment arms:

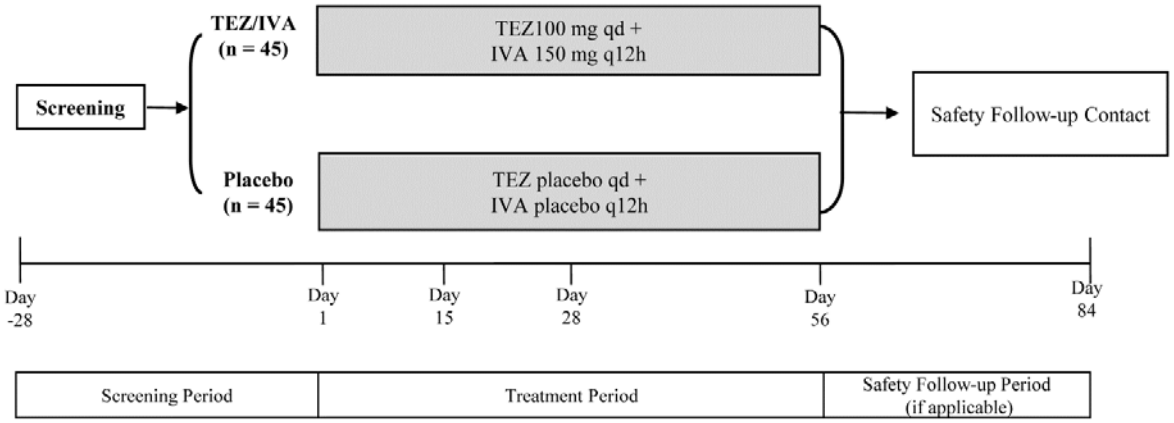
TEZ/IVA: TEZ 100 mg once daily (qd) + IVA 150 mg every 12 hours (q12h)

Placebo: Placebo regimen with visually-matched tablets

Subjects in the United States who complete the Day 56 Visit will be offered the opportunity to receive TEZ/IVA through the Expanded Access Program if they meet the eligibility criteria for that program.

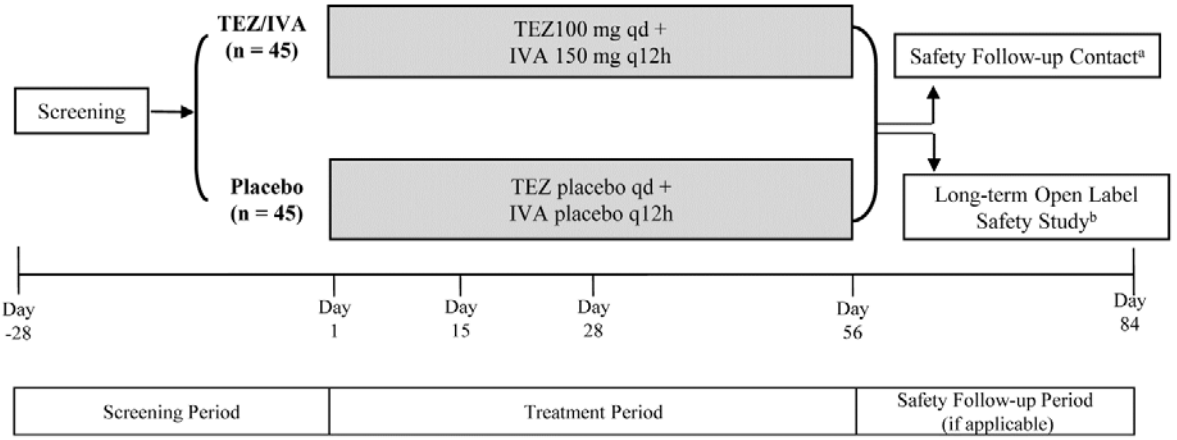
A schematic of the study design is shown in Figure 5-1 and Figure 5-2.

Figure 5-1 Schematic of the Study Design for US subjects



Note: Clinical visits are on Days -28, 1, 15, 28, and 56. A telephone contact on Day 3 collects AEs. The Safety Follow-up may be a clinic visit or telephone call.

Figure 5-2 Schematic of the Study Design for EU subjects



[a] The Safety Follow-up Contact is scheduled to occur 28 (±7) days after the last dose of study drug. The Safety Follow up Contact is not required for subjects who complete the Day 56 Visit and have enrolled in a long-term, open-label safety study of TEZ/IVA within 28 days after the last dose of study drug.

[b] Subjects who complete the Day 56 Visit will be offered the opportunity to enroll in a long-term, open-label safety study of TEZ/IVA if they meet eligibility requirements for the safety study.

Note: Clinical visits are on Days -28, 1, 15, 28, and 56. A telephone contact on Day 3 collects AEs. The Safety Follow-up may be a clinic visit or telephone call.

5.2 Sample Size and Power

Sample size calculation is based on the key secondary endpoint of absolute change in ppFEV$_1$ to the average of the Day 28 and Day 56 measurements.

A Bayesian approach was used to assess the treatment effect on the change in ppFEV$_1$. The study will be considered successful if the posterior probability that the treatment difference between TEZ/IVA and placebo is greater than 0 is at least 80%, using a noninformative prior distribution. Assuming a 3.0 percentage points mean treatment difference between TEZ/IVA and placebo and a standard deviation (SD) of 6.0 percentage points, with 45 TEZ/IVA subjects and 45 placebo subjects, the Bayesian power to achieve the posterior probability criterion is at least 90% (92.6%). After adjusting for an assumed dropout rate of 5% a total sample size of 90 subjects is needed.

[redacted]

5.3 Randomization

Approximately 90 subjects (45 per arm) who meet eligibility criteria will be stratified by age at Screening Visit (<18 versus ≥18 years of age), sex (male versus female), and percent predicted FEV$_1$ severity determined during the Screening Period (<40 versus ≥40), and then randomized (1:1) to either TEZ/IVA or placebo. An interactive web response system (IWRS) will be used for randomization following a list of randomization codes generated by a designated vendor [redacted]

5.4 Blinding and Unblinding

This is a double-blind study.

5.4.1 Blinding

The subjects and all site personnel, including the investigator, the site monitor, and the study team, will be blinded with the exception of the following:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency. Such unblinding events will be fully documented (see below).
- Any site personnel for whom this information is important to ensure the safety of the subject and her fetus in the event of a pregnancy. Such unblinding events will be fully documented (see below).
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations

- Unblinded statistician preparing the final (production) randomization list who is not part of the study team
- Vertex Clinical Operations IWRS management
- Vertex Clinical Supply Chain
- IDMC
- Vendor preparing the unblinded analysis for the IDMC
- Vendor preparing the unblinded interim analysis focusing on safety outcomes

Vertex Medical Monitor may, for matters relating to safety concerns, unblind individual subjects at any time. Such unblinding events will be fully documented (see below).

Spirometry Data Blinding

Despite treatment blinding, knowledge of the spirometry 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 post-dose spirometry data. The vendor for central reading of the spirometry data will send only blinded spirometry files (blinded treatment group, with real values for screening and baseline, but with dummy values for all the spirometry assessment 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 spirometry results during the Treatment Period regardless of whether the subject has prematurely discontinued treatment

5.4.2 Unblinding

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The unblinding method will be either a manual or electronic process.

Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators should use their best judgment as to whether to unblind without first attempting to contact the medical monitor to discuss and agree to the need for unblinding. If investigators deem that it is not necessary to unblind immediately, they will first attempt to contact the medical monitor to discuss and agree to the need for unblinding. If investigators have tried but are unable to reach the medical monitor, they should use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding.

Contact information for the medical monitor (or appropriate backup) will be provided in a separate document.

In addition, the Vertex Medical Information Call Center ([redacted]) will answer calls 24 hours a day, 7 days a week, 365 days of the year, and will triage these calls to the study medical monitor or appropriate backup.

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor should be notified within 24 hours of the unblinding

event. The reason and the date of the unblinding will be documented clearly in the subject's study file. Information about the treatment assignment obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with sponsor (Vertex), contract research organization (CRO), or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS or designee, per Protocol Section13.1.2.

Vertex GPS or designee will also unblind any SAE reports in compliance with regulatory reporting requirements. In addition, the Vertex medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time.

6 ANALYSIS SETS

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

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 the disposition summary table, unless otherwise specified.

The **Randomized Set** is defined as all subjects who have been randomized.

The **Full Analysis Set** (FAS) is defined as all randomized subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug.

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

7 STATISTICAL ANALYSIS

7.1 General Considerations

All individual subject data in the All Subject Set will be presented in data listings. The Schedule of Assessments is provided in Section 10.1. The precision standards are provided in Section 10.6.

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

Categorical variables will be summarized using counts and percentages.

Baseline Value, unless otherwise specified, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to or on the first dose of study drug.

Change (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.

Treatment Emergent (TE) Period will be defined in the following way:

- For patients who complete the Safety Follow-up Contact, the TE period will include the time from the first dose of the study drug to the Safety Follow-up Contact.
- For subjects who discontinue and have an ETT Visit but no Safety Follow-up Contact, the TE period will include the time from the first dose of the study drug until the ETT visit.
- For subjects who withdraw consent, the TE period includes the time from the first dose of the study drug until withdrawal.
- For subjects who enroll in Study VX14-661-110 (EU only) or in the EAP (US only), the TE period in this study (Study 114) will include the time from the first dose of study drug in this study until the earlier of last study participation day OR until 28 days after the last dose of the study drug in Study 114.
- For all other subjects, including those who do not have a Safety Follow-up Contact, the TE period includes the time from the first dose of the study drug until the earlier of last study participation day OR until 28 days after the last dose of the study drug.

Unscheduled Visits: Unscheduled visit measurements will be included in the following:

1. derivations of measurements at scheduled visits per specified visit windowing rules below;
2. derivations of baseline/last on-treatment measurements;
3. derivations of the maximum/minimum on-treatment values and maximum/minimum changes from baseline values for safety analyses;
4. data listings where appropriate.

Visit Windowing Rules: Section 10.2 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 Day 56.
    - 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 Day 56, or remain as SFU if they go beyond the upper boundary of the window for Day 56.

- 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, it will be used according to the nominal visit in relevant analyses.

Note: spirometry assessments (other than Day 1 postdose spirometry) will be used for both efficacy and safety purposes. The measurements will follow the visit windowing rules for efficacy parameters. Day 1 postdose spirometry assessments will be used for safety purposes only.

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.

7.2 Background Characteristics

7.2.1 Subject Disposition

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

- All Subjects Set (randomized or dosed)
- Randomized Set
- Full Analysis Set (FAS)
- Safety Set

The number and percentage of subjects in each of the following disposition categories will be presented by treatment and overall based on the Safety Set:

- Completed treatment through Day 56
- Prematurely discontinued treatment (any tablet) and the reason for discontinuation and day at discontinuation
- Completed study
- Prematurely discontinued the study and the reasons for discontinuations

A listing will be provided for subjects who discontinued treatment or who discontinued from the study, along with reason for discontinuation.

The number and percentage of randomized subjects will be summarized by stratification factor, and by country and by site, using the number of subjects being randomized to each treatment group as the denominator. A randomization listing will be provided with subjects ordered by randomization date.

7.2.2 Demographics and Baseline Characteristics

The following demographic data will be summarized by treatment and overall based on the FAS:

- Age at Baseline
- Sex
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Country (USA, France, Germany)

The following baseline characteristics will be summarized:

- Height (cm) (subjects < 18 years old only)

Stratification categories (in addition to sex) will also be summarized:

- Age groups at screening (< 18, ≥18 years)
- Percent predicted FEV_1 at screening (<40, ≥40)

Disease characteristics at baseline will include the following:

- Percent predicted FEV_1 category (<40, ≥40-<70, ≥70)
- Percent predicted FEV_1
- CFQ-R Respiratory Symptoms domain
- FEV_1 (L)
- FVC (L)
- Percent predicted FVC
- $FEF_{25-75\%}$ (L/sec)
- Percent predicted $FEF_{25-75\%}$
- FEV_1/FVC
- Use of dornase alfa
- Use of inhaled antibiotic
- Use of azithromycin
- Use of any bronchodilator (inhaled or oral)
- Use of inhaled bronchodilator Use of inhaled hypertonic saline
- Use of inhaled corticosteroids

In addition, data listings will also be provided for:

- Informed consent;
- Inclusion/Exclusion criteria violation (for subjects with any such violations);

7.2.3 Medical History

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). For the FAS, medical history will be summarized descriptively by system organ class (SOC) and preferred term (PT). The corresponding data listing will also be provided.

7.2.4 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.

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 7-1:

Table 7-1 Logic for Determining the Category of a Medication

Medication start date	Medication end 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

7.2.5 Study Drug Exposure

Exposure summaries will be based on the FAS.

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

Duration of study drug exposure expressed in weeks will be summarized descriptively (number, mean, SD, median, minimum, and maximum) and also into the following categories: ≤1 weeks, >1-≤4 weeks, >4-≤8 weeks and > 8 weeks. Additionally, the total duration of study drug exposure, defined as the sum of all subjects' duration of treatment exposure and expressed in patient years, will be provided.

7.2.6 Study Drug Compliance

Study drug compliance will be measured by the compliance rate and be summarized based on the FAS.

Compliance rate will be calculated as follows:

100 × [1 - (Total number of days study drug interrupted) / (Duration of study drug exposure)].

The total number of days of study drug interrupted is defined as the sum of (number of unique days of study drug interrupted in each interruption interval), where number of days of 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% of compliance rate will be provided.

7.2.7 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. IPDs 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:

- 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. Additionally, IPDs will be provided as a subject data listing.

7.3 Primary Safety Analysis

7.3.1 Definition of Primary Safety Endpoint

Respiratory safety of TEZ/IVA is the primary objective of this study and will be assessed in terms of incidence, including the following respiratory adverse events of special interest (RAESI) while patients are on treatment:

- Chest discomfort
- Dyspnea (shortness of breath)
- Respiration abnormal (chest tightness)
- Asthma
- Bronchial hyperreactivity
- Bronchospasm
- Wheezing

A summary of RAESI will be presented by PT, relationship and severity.

Treatment Emergent (TE) Period will follow the definition in Section 7.6

7.3.1.1 Summaries of RAESI by Treatment Interval

RAESI will also be summarized by PT for the following treatment intervals:

- 0 -1 Week: [Day 1, Day 7]

- >1 -4 Weeks: [Day 8, Day 28]
- >4 -8 Weeks: [Day 29, Day 56]
- > 8 Weeks: [Day 57, End of TE period]

Separate listings will be presented for RAESI leading to treatment discontinuation, treatment interruption and deaths.

7.4 Primary Efficacy Analysis

The actual Bayesian posterior probability will be calculated for a greater than zero (>0) treatment effect difference in mean $ppFEV_1$ change between TEZ/IVA and placebo, based on the observed absolute change from baseline in $ppFEV_1$ to the average of Day 28 and Day 56. 95% credible intervals will be provided along with the actual Bayesian posterior probability.

7.5 Additional Efficacy Analysis

Unless otherwise defined, all efficacy analyses described in this section will be based on the FAS. The FAS will be used in the summary of demographics and baseline characteristics and analyses of the efficacy data; subjects will be analyzed according to their randomized treatment assignment.

7.5.1 Key Secondary Efficacy Endpoint

7.5.1.1 Definition of Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the absolute change in $ppFEV_1$ from baseline to the average of the Day 28 and Day 56 measurements.

$ppFEV_1$ 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 Wang and Hankinson standards; details are in Section 10.3.

7.5.1.2 Analysis of Key Secondary Efficacy Endpoint

Descriptive summary statistics including:

- Number of subjects (n)
- Mean
- Standard deviation (SD)
- Median
- Minimum and Maximum (Min, Max)

will be provided for the observed values at each study time-point for the absolute of $ppFEV_1$ from baseline at each post-baseline visit (Day 15, Day 28 and Day 56) as well as to the average of Day 28 and Day 56.

Descriptive summary statistics will be reported for both the within-treatment arm change and the between-treatment arm difference of change.

7.5.2 Secondary Efficacy Endpoints

The following are the secondary efficacy endpoints:

- Relative change in $ppFEV_1$ from baseline to the average of Day 28 and Day 56 measurements
- Absolute change in the CFQ-R respiratory domain score from baseline to the average of Day 28 and Day 56 measurements

7.5.2.1 Definition of Secondary Efficacy Endpoints

Relative change in percent predicted FEV_1 from baseline to the average of Day 28 and Day 56 measurements

Relative change in $ppFEV_1$ from baseline to post-baseline measurements will be calculated and expressed in percentage as 100×(Post-baseline $ppFEV_1$- Baseline $ppFEV_1$) / Baseline $ppFEV_1$

Relative change in $ppFEV_1$ from baseline to the average of Day 28 and Day 56 measurements is defined as the average of relative change in percent predicted FEV_1 at Day 28 and Day 56

Absolute change in the CFQ-R respiratory domain score from baseline to the average of Day 28 and Day 56 measurements

Defined as the average of CFQ-R respiratory domain score at Day 28 and Day 56 minus CFQ-R respiratory domain score at baseline

The CFQ-R[1,2,3]is a valid CF-specific instrument that measures quality-of-life domains. This study uses three different versions of CFQ-R forms in this study:

- CFQ-R for Children Ages 12 and 13 has a total of 35 questions to form 8 domains. All questions are scored 1, 2, 3, or 4.
- CFQ-R for Adolescents and Adult (subjects 14 years and older) has a total of 50 questions to form 12 domains. Question 43, which is scored 1, 2, 3, 4, or 5, is not used in calculating any domain; all the other 49 questions are scored 1, 2, 3, or 4.
- CFQ-R for Parents/Caregivers (subjects 13 years and younger) has a total of 44 questions to form 11 domains. Question 37, which is scored 1, 2, 3, 4, or 5, is not used in calculating any domains; all the other 43 questions are scored 1, 2, 3, or 4.

For all 3 CFQ-R versions, to calculate the score for each domain, the response scores on the negatively phrased questions are reversed (reversed scores = 5 – response scores) so that 1 always represents the worst condition and 4 always represents the best condition.

The scaled score for each domain ranges from 0 (worst condition) to 100 (best condition). It is calculated as follows:

Scaled score for a domain = 100 × (mean(scores of all questions in that domain) - 1)/3

The scaled score for a specific domain will not be calculated if more than half of the questions in the domain have missing scores.

Table 7-2, Table 7-3, and Table 7-4 provide the questions included in each domain, the questions with the reversed scores, as well as the maximum number of missing questions for the CFQ-R for Children Ages 12 and 13, the CFQ-R for Adolescents and Adults, and the CFQ-R for Parents/Caregivers respectively. [redacted]

Table 7-2 CFQ-R for Children Ages 12 and 13

Domain	Questions		Reversed questions	Maximum number of missing questions
	Total	Individual		
Physical	6	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5	3
Emotion	8	7, 8, 9, 10, 11, 12, 13, 14	14	4
Social	7	20, 21, 22, 23, 24, 25, 26	20, 22, 24, 26	3
Body	3	27, 28, 29	-	1
Eat	3	15, 17, 19	19	1
Treatment burden	3	16, 18, 30	18	1
Respiration	4	31, 32, 33, 34	-	2
Digestion	1	35	-	0

Table 7-3 CFQ-R for Adolescents and Adults (Subjects 14 Years and Older)

Domain	Questions		Reversed questions	Maximum number of missing questions
	Total	Individual		
Physical	8	1, 2, 3, 4, 5, 13, 19, 20	13	4
Role	4	35, 36, 37, 38	35	2
Vitality	4	6, 9, 10, 11	6, 10	2
Emotion	5	7, 8, 12, 31, 33	-	2
Social	6	22, 23, 27, 28, 29, 30	23, 28, 30	3
Body	3	24, 25, 26	-	1
Eat	3	14, 21, 50	-	1
Treatment burden	3	15, 16, 17	15, 17	1
Health perceptions	3	18, 32, 34	18, 32, 34	1
Weight	1	39	-	0
Respiration*	6	40, 41, 42, 44, 45, 46	43	3
Digestion	3	47, 48, 49	-	1

*: Question 43 not used to calculate a domain.

Table 7-4 CFQ-R for Parents/Caregivers (Subjects 13 Years and Younger)

Domain	Questions		Reversed questions	Maximum number of missing questions
	Total	Individual		
Physical	9	1, 2, 3, 4, 5, 13, 14, 15, 16	15	4
Vitality	5	8, 9, 10, 11, 12	10, 12	2
Emotion	5	6, 7, 23, 25, 26	6	2
School	3	27, 28, 29	28	1
Body	3	19, 20, 21	-	1
Eat	2	17, 44	-	0
Treatment burden	3	18, 30, 31	31	1
Health perceptions	3	22, 24, 32	22, 24, 32	1
Weight	1	33	-	0
Respiration*	6	34, 35, 36, 38, 39, 40	37	3
Digestion	3	41, 42, 43	-	1

*: Question 37 not used to calculate a domain.

7.5.2.2 Additional Secondary Endpoint

Discontinuation rate based on study drug discontinuation through Day 56

Discontinuation rate based on study drug discontinuation through Day 56 is defined (in percentage) as 100 × [the number of subjects who permanently discontinued study drug before Day 56 visit / by the number of subjects in the FAS set].

7.5.2.3 Analysis of Secondary Efficacy Endpoints

Relative change in ppFEV$_1$ from baseline to the average of Day 28 and Day 56 measurements

Analysis for the relative change in ppFEV$_1$ through from baseline to the average of Day 28 and Day 56 measurements will be similar to that for the key secondary endpoint analysis by providing the following descriptive summary statistics:

- Number of subjects (n)
- Mean
- Standard deviation (SD)
- Median
- Minimum and Maximum (Min, Max)

These descriptive summary statistics will be provided for the observed values at each study time-point for the relative change of ppFEV$_1$ from baseline at each post-baseline visit (Day 15, Day 28 and Day 56) as well as to the average of Day 28 and Day 56.

Descriptive summary statistics will be reported for both the within-treatment arm change and the between-treatment arm difference of change.

Absolute change in the CFQ-R respiratory domain score from baseline to the average of Day 28 and Day 56 measurements

Analysis for the absolute change in CFQ-R respiratory domain score (Pooled 'Children Ages 12 and 13' Version and 'Adolescents and Adults' Version) will be similar to that for the key secondary endpoint analysis by providing the following descriptive summary statistics:

- Number of subjects (n)
- Mean
- Standard deviation (SD)
- Median
- Minimum and Maximum (Min, Max)

These descriptive summary statistics will be provided for the observed values at each study time-point for the absolute change in CFQ-R respiratory domain score (Pooled 'Children Ages 12 and 13' Version and 'Adolescents and Adults' Version) from baseline at each post-baseline visit (Day 15, Day 28 and Day 56) as well as to the average of Day 28 and Day 56.

Descriptive summary statistics will be reported for both the within-treatment arm change and the between-treatment arm difference of change.

7.5.2.4 Multiplicity adjustment

No multiplicity adjustment will be made for the analysis of secondary endpoints.

7.5.2.5 Analysis of Additional Secondary Endpoint

Discontinuation rate based on study drug discontinuation through Day 56

Discontinuation rate based on study drug discontinuation through Day 56 will be summarized by the proportions by treatment arms as well as in the overall population.

[redacted]

7.6 Additional Safety Analysis

All safety analyses will be based on the Safety Set. Subjects will be analyzed according to the treatment they actually received if they took the same study drug during the entire study period. For subjects receiving study drug from more than one treatment group by error, the treatment group allocation will be TEZ/IVA.

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 and urinalysis)
- Vital signs
- Pulse oximetry
- Postdose spirometry on Day 1.

Safety endpoints will be analyzed using data during the treatment emergent period. Only descriptive summaries will be presented and no statistical testing is planned.

Treatment Emergent (TE) Period will be defined in the following way:

- For patients who complete the Safety Follow-up Contact, the TE period will include the time from the first dose of the study drug to the Safety Follow-up Contact.
- For subjects who discontinue and have an ETT Visit but no Safety Follow-up Contact, the TE period will include the time from the first dose of the study drug until the ETT visit.
- For subjects who withdraw consent, the TE period includes the time from the first dose of the study drug until withdrawal.
- For subjects who enroll in Study VX14-661-110 (EU only) or in the EAP (US only), the TE period in this study (Study 114) will include the time from the first dose of study drug in this study until the earlier of last study participation day OR until 28 days after the last dose of the study drug in Study 114.
- For all other subjects, including those who do not have a Safety Follow-up Contact, the TE period includes the time from the first dose of the study drug until the earlier of last study participation day OR until 28 days after the last dose of the study drug.

For the purpose of safety analyses, the entire study period will then be further divided into 3 segments:

- The **pre-treatment period** is the period after the informed consent/assent date and before the start date of the TE period.
- The **treatment-emergent period** (TE period) is defined as above.
- The **post-treatment period** is the period after the end of the TE period to the date of the last study record in the clinical database.

7.6.1 Adverse Events

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

- **Pre-treatment 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 a missing or partial start date, if there is no clear evidence that the AEs started (or increased in severity) before or after the first dose date, the start date will be imputed to be the first dose date and the AE will be considered to be a TEAE (see Section 10.7). Similarly, if there is no clear evidence that the AEs started (or increased in severity) before or after the start of the post-treatment period, the start date will be imputed to be the earliest possible time in the TEAE period and the AE will be considered to be a TEAE. As an intermediate step for programming purposes, imputation rules for missing or partially missing AE start/end dates are defined in Section 10.7.

Based on the reported severity and relationship to study drugs, TEAEs can be categorized as follows:

By relationship to the study drugs, treatment emergent adverse events (TEAEs) will be classified into the 4 categories:

- Not related
- Unlikely related
- Possibly related
- Related.

By severity, TEAEs will be classified into the 4 categories:

- **Mild (Grade 1):** Mild level of discomfort and does not interfere with regular activities
- **Moderate (Grade 2):** Moderate level of discomfort and significantly interferes with regular activities
- **Severe (Grade 3):** Significant level of discomfort and prevents regular activities
- **Life-threatening (Grade 4 and 5):** Any adverse drug experience that places the subject, in the view of the investigator, at immediate risk of death.

7.6.1.1 Overview of Pre-treatment AEs and Treatment Emergent AEs

An overview of the pre-treatment AEs will be summarized in the following categories:

- Any pre-treatment AEs
- Grade 3/4 pre-treatment AEs
- Pre-treatment SAEs by severity.

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

- Any TEAEs
- Grade 3/4 TEAEs
- TEAEs by relationship
- TEAEs by severity

- TEAEs leading to treatment discontinuation (this category will capture TEAEs leading to discontinuation of either the morning or the evening tablets)
- TEAEs leading to treatment interruption (this category will capture TEAEs leading to interruption of either the morning or the evening tablets)
- Related TEAEs
- Serious TEAEs (TE SAEs)
- TE SAEs by relationship
- TE SAEs by severity
- Related serious TEAEs
- TEAE leading to death

7.6.1.2 TEAEs and TE SAEs by System Organ Class (SOC) and Preferred Term (PT)

The number and percentage of subjects with TEAEs will be summarized by treatment group, MedDRA system organ class (SOC), and preferred term (PT), where multiple occurrences of the same AE for the same subject will be counted only once. The summary table will be presented in descending order of frequencies in the TEZ/IVA treatment group. TE SAEs will be summarized similarly.

7.6.1.3 TEAEs and TE SAEs by Preferred Term (PT)

The number and percentage of subjects with TEAEs will be summarized by treatment group and PT, where multiple occurrences of the same AE for the same subject will be counted only once. The summary table will be presented in descending order of frequencies in the TEZ/IVA treatment group. TE SAEs will be summarized similarly.

7.6.1.4 TEAEs and TE SAEs by SOC, PT, and Relationship

The number and percentage of subjects with TEAEs will be summarized by treatment group, SOC, PT, and relationship, where multiple occurrences of the same AE for the same subject will be counted only once according to the worst relationship to study drug. The summary table will be presented in descending order of frequencies in the TEZ/IVA treatment group. TE SAE will be summarized similarly.

7.6.1.5 TEAEs and TE SAEs by SOC, PT, and Severity

The number and percentage of subjects with TEAEs will be summarized by treatment group, SOC, PT, and severity, where multiple occurrences of the same AE for the same subject will be counted only once according to the worst severity. The summary table will be presented in descending order of frequencies in the TEZ/IVA treatment group. TE SAE will be summarized similarly.

7.6.1.6 Elevated Transaminase

The following AE preferred terms will be selected for **elevated transaminase**:

- Alanine aminotransferase abnormal
- Alanine aminotransferase increased
- Aspartate aminotransferase abnormal
- Aspartate aminotransferase increased
- Transaminases abnormal
- Transaminases increased
- Liver function test abnormal
- Liver function test increased
- Hypertransaminasaemia
- Hepatic enzyme abnormal
- Hepatic enzyme increased.

A summary of elevated transaminase will be presented by preferred term.

Separate listings will be presented for TEAEs leading to treatment discontinuation, treatment interruption, TE SAEs, and all deaths.

For all AEs, the CRF captures the action taken for TEZ/IVA pills separately from the AE action taken for IVA monotherapy pills. As a result, it is possible that, in the final database (after DBL), the AE actions taken for the two agents (fixed dose TEZ/IVA and IVA monotherapy) are different. The summaries and listings of "AE Leading to Treatment Discontinuation" and "AE Leading to Treatment Interruption" account for discontinuation and interruptions for either agent.

7.6.2 Clinical Laboratory Values

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

The number and percentage of subjects with hematology, chemistry and coagulation values meeting the defined threshold criterion will be summarized by treatment, lab parameters, and visit. The threshold criteria are provided in Section 10.5, Table 10-8 and Table 10-9.

In addition, a listing containing individual subject hematology, chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from

scheduled and unscheduled time points. Subjects with positive pregnancy test results will be listed. Abnormal urinalysis results also will be listed by treatment and subject.

7.6.3 Vital Signs

For treatment emergent vital signs measurements, the raw values and changes from baseline will be summarized by treatment group at each scheduled time point for systolic and diastolic blood pressure (mmHg), HR (beats per minute), and respiratory rate (breaths per minute). In addition, the mean value at each time point will be plotted by treatment group for systolic and diastolic blood pressure.

The number and percentage of subjects with vital signs meeting threshold criteria during the treatment-emergent period will be summarized by treatment, vital signs parameters, and visit. The threshold criteria are provided in Section 10.5, Table 10-7.

7.6.4 Pulse Oximetry

A summary of raw values and change from baseline values will be provided by treatment group at each scheduled time point for the percent of oxygen saturation by pulse oximetry. In addition, the mean value at each visit will be plotted by treatment group for the percent of oxygen saturation.

The number and percentage of subjects with shift changes from baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the treatment-emergent period will be tabulated by treatment groups.

7.6.5 Postdose Spirometry on Day 1

For the 2-hour and 4-hour postdose measurements on Day 1, a summary of raw values and absolute change from predose percent predicted FEV_1 will be provided by treatment at Day 1. The absolute change from the Day 1 predose value of percent predicted FEV_1 will be summarized by treatment at each time point. In addition, the number and percentage of subjects with percent predicted FEV_1 decline of $\geq$10, $\geq$15, and $\geq$20 percentage points in the absolute change from the Day 1 predose value will be summarized by treatment and by assessment time. Subjects with percent predicted FEV_1 decline $\geq$10 percentage points will be listed.

7.6.6 Physical Examination

Abnormal PE findings will be presented in a data listing only.

8 INTERIM AND DMC ANALYSES

8.1 Interim Analysis

8.2 No interim analysis is planned for this study. DMC Analysis

An independent data monitoring committee (IDMC) was formed before study initiation. The IDMC's objectives and operational details were defined in a separate document (IDMC Charter) which was finalized before the first subject was screened in the study. The IDMC conducted regular planned safety reviews of study data as outlined in the IDMC Charter and IDMC Analysis Plan. The first DMC analysis will be performed when approximately 50% of subjects have completed their Day 56 visit at the same time of the planned interim analysis.

9 REFERENCES

[1] Quittner AL, Modi A, Cruz I. Systematic review of health-related quality of life measure for children with respiratory conditions. Pediatr Respir Rev. 2008;9:220-32.

[2] Goss C, Quittner AL. Patient-reported outcomes in cystic fibrosis. Proc Am Thorac Soc. 2007;4:1-9.

[3] Modi AC, Quittner AL. Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis. J Pediatr Psychol. 2003;28(8):535-45.

[4] Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999; 159:179-87.

[5] Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol. 1993; 15:75-88.

10 APPENDICES

10.1 Schedule of Assessments

Table 10-1 Study VX16-661-114: Screening

Event/Assessment	Screening Visit Day -28 to Day -1
Informed consent and assent (when applicable)	X
Demographics	X
Medical history	X
CFTR genotype[a]	X
Ophthalmologic examination[b]	X
Prior and concomitant medications[c]	X
Height and weight (measured with shoes off)	X
Vital signs[d]	X
Pulse oximetry[d]	X
Physical examination of all body systems	X
Serum FSH[e] (amenorrheic female subjects only)	X
Serum pregnancy test[f]	X
Safety labs[g]	X
Spirometry[h]	X
Inclusion/exclusion criteria review	X
AEs and SAEs	Continuous from signing of informed consent form (ICF) and assent (where applicable) through Safety Follow-up Contact

AE: adverse event; CFTR: cystic fibrosis transmembrane conductance regulator;; FSH: follicle-stimulating hormone; ICF: informed consent form; SAE: serious adverse event

[m] For enrolled subjects who do not have a Safety Follow-up Contact, AEs and SAEs will be collected through the earliest of either 28 days after the last dose of study drug, or the ETT Visit (if that visit is 3 weeks or later following the last dose of study drug; see Section 9.1.4).

[a] Only if the *CFTR* genotype is not documented in the subject's medical record.

[b] An ophthalmologic examination is required for subjects <18 years who did not have an ophthalmologic examination prior to starting Orkambi if they have not have one within 6 months prior to the Screening Period. Subjects who have documentation of bilateral lens removal do not need an ophthalmologic exam (protocol section 11.4.7).

[c] All medications taken within 28 days before the Screening Period through the end of the study will be recorded.

[d] Vital signs (pulse rate, blood pressure, and respiration rate) and pulse oximetry will be collected after the subject has been at rest in the seated or supine position for at least 5 minutes.

[e] FSH will be measured for any potentially postmenopausal female with at least 12 months of continuous spontaneous amenorrhea.

[f] 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 (See protocol section 11.4.4.1).

[g] Includes serum chemistry, hematology, coagulation and urinalysis.

[h] Spirometry may be performed pre- or post-bronchodilator (See protocol section 11.3.1). Screening spirometry evaluation may be repeated, as specified in protocol section 9.1.1.1.

Table 10-2 Study VX16-661-114: Treatment Period, ETT, and Safety Follow-up Contact Assessments

Event/Assessment[i]	Day 1	Day 3 Telephone Contact[j]	Day 15 (± 3 Days)	Day 28 (± 5 Days)	Day 56 (± 5 Days)	Early Termination of Treatment[k]	Safety Follow-up Contact 28 (± 7) Days After Last Dose of Study Drug[l]
Inclusion and exclusion criteria review	X		X	X	X		
Randomization[m]	X						
Clinic visit	X		X	X	X	X	
CFQ-R[n]	X		X	X	X	X	
Spirometry[o]	X		X	X	X	X	
Height (<18 years old only)	X		X	X	X	X	
Vital signs[p]	X		X	X	X	X	
Pulse oximetry[h]	X		X	X	X	X	
Physical examination[q]	X					X	
Pregnancy test	urine		urine	urine	serum	serum	
Safety labs[r]	X		X		X	X	

[i] All assessments will be performed before dosing unless noted otherwise

[j] On Day 3, there is a telephone contact to collect AEs.

[k] If the subject prematurely discontinues study drug treatment, an ETT Visit should be scheduled as soon as possible after the decision to terminate study treatment. Subjects who prematurely discontinue study drug treatment will also be required to complete the Safety Follow-up Contact, approximately 28 (± 7) days after their last dose of study drug. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Contact, and a separate Safety Follow-up Contact will not be required. See protocol section 9.1.4.

[l] Telephone contact may be acceptable. A clinic visit may be required at the discretion of the investigator. The Safety Follow up Visit is not required for subjects who complete the Day 56 Visit and enroll in a long-term, open-label safety study of TEZ/IVA within 28 days after the last dose of study drug.

[m] Randomization must occur after all inclusion and exclusion criteria are met and before the first dose of study drug. Randomization will be done through IWRS. Randomization may occur on Day -1.

[n] The CFQ-R must be completed as the first assessment at each visit.

[o] Predose spirometry must be performed before dosing and should be performed prebronchodilator at all visits. Postdose spirometry will be performed at 2 hours (± 30 minutes) and 4 hours (± 30 minutes) after dosing on Day 1 only.

[p] Vital signs (pulse rate, blood pressure, and respiration rate) and pulse oximetry will be collected after the subject has been at rest in the seated or supine position for at least 5 minutes.

[q] In addition to the complete PEs indicated, symptom-targeted PEs may occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

[r] Includes serum chemistry, hematology, coagulation and urinalysis.

Table 10-2 Study VX16-661-114: Treatment Period, ETT, and Safety Follow-up Contact Assessments

Event/Assessment[i]	Day 1	Day 3 Telephone Contact[j]	Day 15 (± 3 Days)	Day 28 (± 5 Days)	Day 56 (± 5 Days)	Early Termination of Treatment[k]	Safety Follow-up Contact 28 (± 7) Days After Last Dose of Study Drug[l]
Snack or meal at site[s]	X		X	X	X		
Study drug dosing[t]	X		X	X	X		
Study drug count	X		X	X	X	X	
Concomitant medications	X		X	X	X	X	X
Concomitant treatment and procedures review	X		X	X	X	X	X
AEs and SAEs	Continuous from signing of the ICF and assent (where applicable) through the Safety Follow-up Contact[u]						

[s] Fat-containing food such as a "standard CF" high-fat, high-calorie meal or snack will be provided at the site to subjects after all predose assessments have occurred.

[t] On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. At the discretion of the Investigator, subjects may be asked to remain at the site for up to 6 hours after receiving the first dose of study drug on Day 1.

[u] For enrolled subjects who do not have a Safety Follow-up Contact, AEs and SAEs will be collected through the earliest of either 28 days after the last dose of study drug, or the ETT Visit (if that visit is 3 weeks or later following the last dose of study drug). For subjects who complete the study and enroll in a long-term, open-label safety study of TEZ/IVA, AEs and SAEs will be collected through before the first dose of study drug in the safety study.

10.2 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)
• Height (<18 years only) • CFQ-R • Pregnancy test • Vital signs • Pulse oximetry • Spirometry • Safety Labs	Baseline	1	[screening visit, pre-dose Day 1]
	Day 1 Predose and Postdose (only for Spirometry)	1	[1,1]
	Day 15	15	[2, 22]
	Day 28 (safety labs not collected)	29	[23,43]
	Day 56	57	[44,78]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up (SFU)	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 (only for concomitant medications and treatments) 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. Spirometry are following the efficacy windowing rules.

10.3 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[1] and Wang[2] 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. Subjects in whom the Wang standard is applied at the Screening Visit will have the Wang standard applied throughout the study, even if there is a change in age during the course of the study that would otherwise necessitate use of the Hankinson standard.

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 10-4.

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 10-5 and Table 10-6.

If either height or age is missing, and the spirometry measurement is non-missing, the last non-missing value of height and age will be used in the calculation of predicted values.

Table 10-4 HNVs Equation Coefficients by Sex, Race, and Age

Parameter	Sex	Race	Age (years)	b_o	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 4. (Tables 4, 5 and 6)

Table 10-5 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 5. (Tables 2 and 3)

Table 10-6 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 5. (Tables 4 and 5)

10.5 Threshold Analysis Criteria

Table 10-7 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
Glucose	Hypoglycemia <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

Table 10-7 Threshold Criteria for Clinical Chemistry and Hematology

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
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

Table 10-7 Threshold Criteria for Clinical Chemistry and Hematology

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 - ≤155 mmol/L >155 - ≤ 160 mmol/L >160	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
Glucose	Hypoglycemia <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

Table 10-7 Threshold Criteria for Clinical Chemistry and Hematology

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 <0.74 – ≥ 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 >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) (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	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

Table 10-7 Threshold Criteria for Clinical Chemistry and Hematology

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 10-8 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 10-9 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 and >10 mmHg increase from baseline	
	>140 mmHg and >20 mmHg increase from baseline	
	>160 mmHg and >10 mmHg increase from baseline	
	>160 mmHg and >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	

10.6 Standards for Efficacy and Safety Variable Display in TFLs

Table 10-10 Precision Standards for Efficacy Variables

Variable Statistics	Number of Decimal Places
$ppFEV_1$ (%, absolute or relative change)	
Mean, LS mean, 95% CI	1
CFQ-R	
Mean, LS mean, 95% CI	1
Number of events	0
Event rate	2

Number of decimal places for standard error and standard deviation will be the same as that for the corresponding mean.

Table 10-11 Standard Display Units in Percent Predicted FEV_1

Variable	Unit	Displayed Unit
$ppFEV_1$	percent	N/A
Absolute change in $ppFEV_1$	percent	Percentage points
Relative change in $ppFEV_1$	percent	%

10.7 Imputation Rules for Missing AE Start Date

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.