VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX16-661-115, Version 1.0

A Phase 3, Double-blind, Parallel-group Study to Evaluate the Efficacy and Safety of Tezacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, Homozygous or Heterozygous for the *F508del-CFTR* Mutation

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1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
bpm	beats per minute
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
CRF	case report form
CRO	contract research organization
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	full analysis set
FDC	VX-661 100-mg/IVA 150-mg fixed-dose tablet
$FEF_{25-75\%}$	forced expiratory flow, midexpiratory phase
FEV_1	forced expiratory volume in 1 second
F/F	homozygous for *F508del*
F/RF	heterozygous for *F508del* and a second allele with a residual function mutation
FVC	forced vital capacity
IVA	ivacaftor
LS means	Least squares means
LFT	liver function test
max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum value
MMRM	mixed model repeated measure
N	number of subjects
PD	pharmacodynamic/pharmacodynamics
PK	pharmacokinetic/pharmacokinetics
$ppFEV_1$	percent predicted FEV_1
PT	preferred term
q12h	every 12 hours
QRS	Q, R, and S-wave define the QRS-complex in an ECG
QT	QT interval: The duration of ventricular depolarization and subsequent repolarization; it is measured from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate with Fridericia's correction

Abbreviation	Term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
ULN	upper limit of normal
WHODD	World Health Organization Drug Dictionary Enhanced

4 INTRODUCTION

This statistical analysis plan (SAP) Methods, which describes the planned analyses for Study VX16-661-115, is based on the most recent approved clinical study protocol (CSP), the most recent approved electronic case report form (eCRF), and the most recent approved eCRF completion guidelines.

Study VX16-661-115 is a Phase 3, double blind, parallel-group study to evaluate the efficacy and safety of tezacaftor (TEZ; VX 661) in combination with ivacaftor (IVA; VX 770) in subjects aged 6 through 11 years with cystic fibrosis (CF), homozygous or heterozygous for the *F508del-CFTR* mutation.

This SAP (Methods) documents the planned final statistical analyses of efficacy and safety endpoints defined in the VX16-661-115 study protocol. It also documents analyses for additional efficacy and safety variables not specified in the protocol.

[redacted]

The Vertex Biometrics Department or designee will perform the statistical analysis of the efficacy and safety data; SAS (Version 9.4 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the final clinical database 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.

5 STUDY OBJECTIVES

5.1 Primary Objective

To evaluate the efficacy of TEZ/IVA in subjects with CF aged 6 through 11 years, homozygous or heterozygous for *F508del*.

5.2 Secondary Objectives

To evaluate the safety of TEZ/IVA in subjects with CF aged 6 through 11 years, homozygous or heterozygous for *F508del*.

6 STUDY ENDPOINTS

6.1 Primary Endpoint

Absolute change in lung clearance index$_{2.5}$ ($LCI_{2.5}$) from baseline through Week 8

6.2 Secondary Endpoints

- Absolute change from baseline in sweat chloride at Week 8
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline through Week 8
- Safety and tolerability as measured by adverse events (AEs), clinically significant changes in laboratory values (serum chemistry, hematology, coagulation studies, lipids, vitamin levels, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, serial lung function measurement (post-dose spirometry), and ophthalmologic examinations.

7 STUDY DESIGN

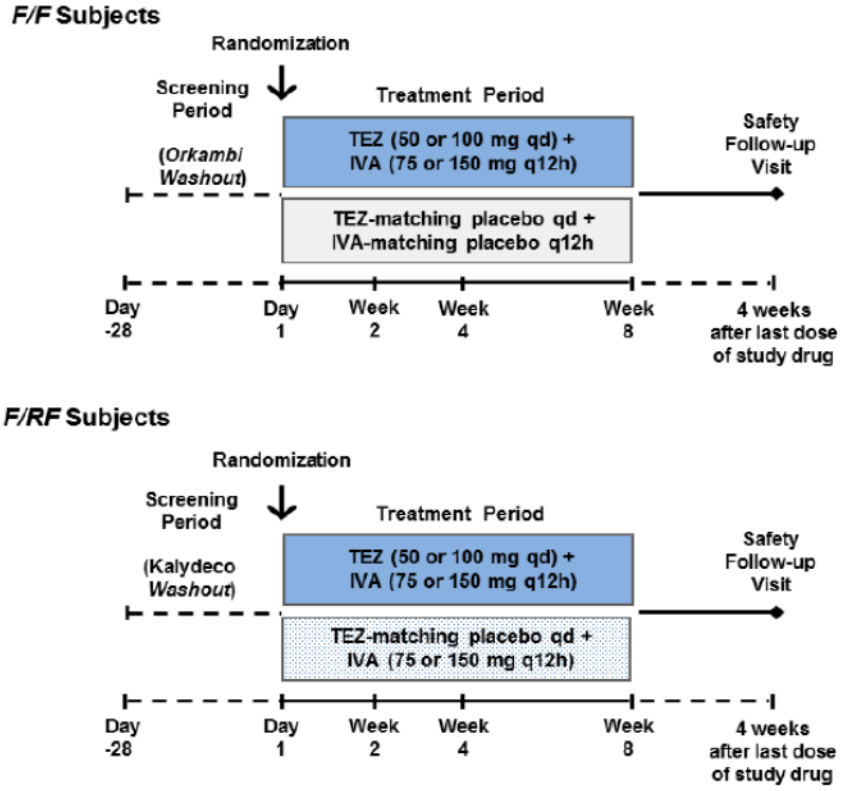
7.1 Overall Design

This is a Phase 3, double-blind, parallel-group study in subjects with CF aged 6 to 11 years, homozygous or heterozygous for *F508del*. Subjects will be:

- homozygous for *F508del* (F/F), or
- heterozygous for *F508del* and a second allele with a residual function mutation (F/RF).

A schematic of the study design is shown in Figure 6-1.

Figure 7-1 VX16-661-115 Study Design



Notes: Subjects who are taking commercially available CFTR modulators (Orkambi or Kalydeco) are required to washout for 28 days before the Day 1 Visit. The study will enroll a total of approximately 65 subjects, of which up to 15 subjects have an F/RF genotype. Subjects will be stratified by genotype group (F/F or F/RF) and randomized 4:1 (TEZ/IVA: blinding arm) before receiving the first dose of study drug on Day 1. The blinding treatment arm will be placebo for F/F subjects and IVA monotherapy (with TEZ-matching placebo) for F/RF subjects. Study drug dose is determined based on weight on Day 1 (<40 kg or ≥40 kg). Subjects will receive matched TEZ/IVA placebo or IVA placebo tablets as appropriate. See Table 9-2 for additional information on study drug tablets and dosing.

7.2 Sample Size and Power

The sample size of this study is driven by demonstrating that the treatment effect of TEZ/IVA excludes a maximum possible placebo effect, which is based on a within-group comparison (change from baseline in $LCI_{2.5}$ in subjects on TEZ/IVA). If the corresponding 2-sided 95% CI of the change from baseline in $LCI_{2.5}$ in subjects on TEZ/IVA excludes the pre-defined maximum possible placebo effect, it will be considered that the study has achieved its primary objective.

A placebo effect is not expected with LCI, because clinical data from other Vertex CFTR modulator studies consistently demonstrated a worsening of lung function (i.e., an increase from baseline in LCI) in the absence of CFTR modulator treatment. Study VX14-809-109 (Study 809-109) evaluated treatment with LUM/IVA in F/F subjects aged 6 through 11 years using change from baseline in LCI as the primary efficacy endpoint and provided the most relevant clinical LCI data available in the younger age group of CF subjects. In Study 809-

109, the placebo group had a mean worsening in $LCI_{2.5}$ of 0.08 units with an SD of 1.41 (higher numbers indicate a worsening of an LCI measurement); the one-sided 90% lower bound was -0.10 and is used as an estimate for the pre-defined maximum possible placebo effect for Study 115.

Accounting for a 10% dropout rate, approximately 40 subjects in the TEZ/IVA group will provide at least 90% power to exclude -0.10 if the true mean change is -0.9 with an SD of 1.41 using a two-sided alpha of 0.05. The current estimate of the maximum possible placebo effect is based on Study 809-109 placebo data in pediatric F/F subjects with CF.

7.3 Randomization

Approximately 65 subjects, of which up to 15 subjects have F/RF genotypes, will be stratified by genotype and randomized 4:1 to study drug treatment.

An interactive web or voice response system (IXRS) will be used to assign subjects to treatment. Detailed instructions for randomization will be provided separately.

7.4 Blinding and Unblinding

Refer to Section 10.8 of the CSP for details.

8 ANALYSIS SETS

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

8.1 All Subjects Set

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

8.2 Full Analysis Set

The Full Analysis Set (FAS) will be defined as all subjects who were randomized and received at least 1 dose of study drug and had an eligible genotype. The FAS will be used for all efficacy analyses and subjects will be analyzed according to the treatment arm they are randomized to.

8.3 Safety Set

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

9 STATISTICAL ANALYSIS

9.1 General Considerations

The Schedule of Assessments is provided in the clinical study protocol (CSP) Table 3-1. Individual subject data for subjects in the All Subjects Set will be presented in individual subject data listings. The precision standards are provided in Appendix B.

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

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 include the time from the first dose to 28 days after the last dose of the study drug or to the completion of study participation date, whichever occurs first. Completion of study participation is defined as one of the following:

- For subjects who complete the study and enroll in the extension study within 28 days of the Week 8 Visit: the last participation date
- For subjects who complete the study and do not enroll in the extension study within 28 days of the Week 8 Visit: the Safety Follow-up Visit
- For subjects who prematurely discontinue study drug treatment but do not withdraw consent: the latest of ETT Visit, or Safety Follow-up Visit (if required)
- For subjects who withdraw consent: date of withdrawal of consent

The TE period will be used for safety analyses unless specified otherwise.

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

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

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

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

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

Multiplicity: No multiplicity adjustment will be performed for hypothesis testing.

9.2 Background Characteristics

9.2.1 Subject Disposition

The number of subjects in the following categories will be summarized overall and by treatment group based on the All Subjects Set:

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

The number and percentage of subjects in each of the following disposition categories will be summarized overall and by treatment group:

- Completed study drug treatment
- Prematurely discontinued the treatment and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation
- Enrolled in a rollover extension study

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

9.2.2 Demographics and Baseline Characteristics

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

Demographic data will include the following:

- Age at screening (years)
- Sex (female and male)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, not collected per local regulations, and Other)

- Geographic region (Europe and Australia)

Baseline characteristics will include the following:

- Mutation (F/F, F/RF)
- Weight group (<40 kg, >=40 kg)
- BMI (kg/m^2)
- BMI z-score
- Weight (kg)
- Weight z-score
- Height (cm)
- Height z-score

Disease characteristics will include the following:

- Baseline $LCI_{2.5}$
- Baseline $ppFEV_1$
- Baseline FEV_1
- Baseline score of CFQ-R respiratory domain
- Baseline sweat chloride

In addition, the following data listings will also be provided:

- Informed consent
- Subjects with any inclusion and exclusion criteria violation

9.2.3 Medical History

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

Based on 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.

9.2.4 Prior and Concomitant Medications

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

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

A given medication may be classified as follows: prior, concomitant, post-treatment, both prior and concomitant, both concomitant and post-treatment, or prior, concomitant, and post-treatment.

If a medication has a completely missing or partially missing start date or stop date and it cannot be determined whether it was taken before the first dose date, concomitantly, or after the TE period, it will be classified as prior, concomitant, and post-treatment.

Prior medications and concomitant medications will be summarized descriptively by: 1) preferred name (PN); and 2) anatomic class (ATC) level 1, ATC level 2, and PN, on the FAS and presented by treatment group and overall. They will also be listed for each subject.

Details for imputing missing or partial start and/or stop dates of medication are described in Appendix D.

9.2.5 Study Drug Exposure

Study drug exposure will be summarized based on the Safety Set, and presented by treatment group and overall.

Duration of study drug exposure (in days) will be calculated as: last dose date – first dose date + 1 day, regardless of study drug interruption.

Duration of study drug exposure will be summarized descriptively (n, mean, SD, median, minimum, and maximum). It will also be summarized in categories for exposure duration: >0 to ≤2 weeks, >2 to ≤4 weeks, >4 to ≤8 weeks, and >8 weeks, using counts and percentages. Additionally, the total study drug exposure, defined as the sum total of the study drug exposure across all subjects (in patient-weeks), will be provided.

9.2.6 Study Drug Compliance

Study drug compliance will be summarized based on the FAS, and presented by treatment group and overall.

Study drug compliance will be calculated as: 100 × [1 − (total number of days of any study drug interruption) / (duration of study drug exposure in days)].

Study drug compliance will be summarized descriptively (n, mean, SD, median, minimum, and maximum), and also in categories: <80% and ⩾80% using frequency and percentage.

9.2.7 Important Protocol Deviations

Important protocol deviations (IPD) are a subset of protocol deviations that may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. IPD rules will be developed and finalized before 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 drug for non-safety reason

- Subject received prohibited concomitant medications
- Subject received the wrong treatment or incorrect doses
- Subject remained in the study despite meeting withdrawal criteria

Occurrence of any of these events should be considered as potential IPDs, but a blinded team should categorize them as IPDs only if they have the potential to significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

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

9.3 Efficacy Analysis

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

All efficacy analyses described in this section will be based on the FAS, unless otherwise specified. The analysis will include all available measurements through the last scheduled on-treatment visit, including measurements after treatment discontinuation.

9.3.1 Analysis of the Primary Efficacy Variable

The primary efficacy endpoint is the absolute change in $LCI_{2.5}$ from baseline through Week 8. The objective of the primary efficacy endpoint analysis is to demonstrate that the mean absolute change from baseline in $LCI_{2.5}$ through Week 8 excludes a pre-defined maximum placebo effect in subjects in the TEZ/IVA group.

The primary analysis will be performed using a restricted maximum likelihood (REML)-based mixed-effect model for repeated measures (MMRM) for the subjects in the TEZ/IVA treatment group in the FAS population. The model will include absolute change from baseline in $LCI_{2.5}$ (including all measurements up to Week 8 [inclusive], both on treatment measurements and measurements after treatment discontinuation) as the dependent variable, and visit (as a class variable) as a fixed effect, with adjustment for mutation group based on the second *CFTR* allele (F/F and F/RF) and baseline $LCI_{2.5}$ (continuous) value as covariates, and subject as a random effect. An unconstructed covariance structure will be used to model the within-subject errors. If the model fails to converge, a compound symmetry covariance structure will be considered. The degrees of freedom of the denominator will be approximated by the Kenward-Roger's method [2].

The primary results obtained from the model will be the estimated average treatment effect through Week 8 in $LCI_{2.5}$ for subjects on TEZ/IVA. The corresponding LS mean, standard error (SE), 95% CI, and p-value will be provided. If the upper bound of the 95% CI is below the pre-defined maximum possible placebo effect, which was specified in the protocol, it will be considered that the study has achieved its primary objective. Summary statistics for change from baseline in $LCI_{2.5}$ through Week 8, and at each visit will also be provided for subjects in the TEZ/IVA treatment group by mutation groups and overall.

For F/F subjects in the placebo treatment group, summary statistics will be provided for change from baseline in $LCI_{2.5}$ through Week 8, and at each visit.

9.3.2 Analysis of Secondary Efficacy Variables

Absolute change in sweat chloride from baseline at Week 8

A similar MMRM model will be used for the above variable using the same approach as described for the analysis of the primary efficacy variable, with the addition of baseline sweat chloride as a covariate. The assessment of efficacy will be primarily based on the estimated mean change from baseline at Week 8.

Similar summary tables will also be provided using the same approach as described for the analysis of the primary efficacy variable.

Absolute change in the CFQ-R respiratory domain score from baseline through Week 8

A similar MMRM model will be used for the CFQ-R respiratory domain score based on the children's version, using the same approach as described for the analysis of the primary efficacy variable, with the addition of baseline CFQ-R respiratory score as a covariate.

Summary tables will also be provided for both the children's version and the parents/caregivers' version using the same approach as described for the analysis of the primary efficacy variable.

[redacted]

[redacted]

9.4 Safety Analysis

All safety analyses will be based on the Safety Set. Subjects will be analyzed according to the treatment they actually received. Only descriptive analysis of safety will be performed (i.e., no statistical hypothesis testing will be performed). The safety endpoints will be summarized using descriptive summary statistics by treatment group and overall. Due to the small sample size, the summary on F/RF subjects treated with IVA and F/F subjects treated with placebo should be interpreted with caution.

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

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry
- Ophthalmologic examination
- Serial lung function (post-dose spirometry)

9.4.1 Adverse Events

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

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

TEAE: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug through the end of the TE period.

Post-treatment AE: any AE that worsened (either in severity or seriousness) or that was newly developed beyond the TE period.

For AEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs started before or after study treatment, the AEs will be classified as TEAEs.

Details for imputing missing or partial AE start/end dates are defined in Appendix E.

9.4.1.1 Overview of TEAEs

An overview table of TEAEs will be provided with the following categories:

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

In addition, a listing containing individual subject adverse event data for TEAEs leading to treatment discontinuation, treatment interruptions, SAEs and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.
For all AEs, the action taken on the CRF for TEZ/IVA (AM dose) is collected separately from the AE action taken for IVA (PM dose). As a result, it is possible that in the AE dataset, the AE actions taken for the two agents are different. The summaries of TEAEs Leading to Treatment Discontinuation or Interruptions account for discontinuation and interruptions for either agent.

9.4.1.2 TEAEs by SOC and PT

In addition, the following summary tables of TEAEs will be provided:

- All TEAEs
- Related TEAEs
- Grade 3/4 TEAEs
- Serious TEAEs
- Related serious TEAES
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- TEAEs leading to death

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

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

9.4.1.3 TEAEs and SAEs by PT

The number and percentage of subjects with TEAEs and SAEs will be summarized by PT, where multiple occurrences of the same adverse event or a continuing adverse event for the same subject will be counted once.

9.4.1.4 Respiratory Events and Symptoms

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

- Chest discomfort
- Dyspnoea
- Respiration abnormal

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

- Asthma
- Bronchial hyperreactivity
- Bronchospasm
- Wheezing

Summary tables of respiratory symptoms and events will be provided by PT.

9.4.1.5 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 table will be provided for elevated transaminases events by PT.

9.4.2 Clinical Laboratory

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

The number and percentage of subjects with events meeting threshold criteria laboratory event during the TE period will be summarized by treatment group and overall. The threshold analysis criterion shift from baseline will also be summarized for selected laboratory parameters. The threshold criteria are provided in Appendix G.

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

In addition, a listing of each subject's liver function test (LFT), non-LFT chemistry, hematology, vitamin, lipid, and coagulation results outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled visits.

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

- A listing of subjects with elevated LFT results during the TE period will be presented. For each subject in the listing, LFT assessments at all the time points will be included (scheduled and unscheduled).
- Mean values (± SD) will be plotted by visit, and box plots of the LFT values/ULN will be plotted by visit.

Summary tables for the shift from baseline to the value at Week 8 will be provided for vitamin levels and the lipid panel. Box plots of vitamin levels and the lipid panel will also be plotted against visit.

9.4.3 Electrocardiogram

For treatment-emergent ECG measurements, a summary of raw values and change from baseline values will be provided at each scheduled time point for the following standard 12-lead ECG measurements: RR (msec), HR (beats per minute [bpm]), PR (msec), QRS duration (msec), QT (msec), and QT corrected for HR intervals (QTcF [msec]). A corresponding listing will also be provided.

The number and percentage of subjects with at least 1 ECG event that meets the threshold criteria during the TE period will be summarized by time point. A corresponding listing will also be presented. This listing will include both scheduled and unscheduled visits. The threshold value criteria are provided in Appendix G.

9.4.4 Vital Signs

For treatment-emergent vital signs measurements, the raw values and change from baseline values will be summarized at each scheduled time point for the following measurements: systolic and diastolic blood pressure (mm Hg), body temperature (°C), HR (bpm), and respiration rate (breaths per minute). A corresponding listing will also be provided.

The number and percentage of subjects with vital sign parameters that meet the threshold criteria during the TE period will be summarized for each scheduled time point. The threshold value criteria are provided in Appendix G.

9.4.5 Pulse Oximetry

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

9.4.6 Physical Examination

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

9.4.7 Ophthalmologic Examination

Ophthalmologic examination findings will be presented as a data listing.

9.4.8 Other Safety Analysis

9.4.8.1 Serial Lung Function (Post-dose Spirometry)

For the 2-hour and 4-hour post-dose spirometry measurements on Day 1 and Week 2, a summary of raw values and the absolute change from the predose value for $ppFEV_1$ will be provided at each time point.

The number and percentage of subjects with $ppFEV_1$ decline $\geqslant$10, $\geqslant$15, and $\geqslant$20 percentage points in the absolute change from baseline in predose value will be summarized for scheduled visits.

In addition, the number and percentage of subjects with $\geqslant$0.10 L or $\geqslant$0.20 L decrease in the absolute change from baseline through Week 8 for FEV1 will also be summarized for scheduled visit.

Subjects with $\geqslant$10 percentage points decrease in absolute change from baseline through Week 8 for $ppFEV_1$ or $\geqslant$0.10 L decrease in the absolute change from baseline through Week 8 for FEV_1 will be listed.

10 INTERIM AND DMC ANALYSIS

10.1 Interim Analysis

No formal interim analysis is planned.

10.2 DMC Analysis

An independent data monitoring committee (IDMC) was formed before study initiation to review the safety of the study. 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.

11 REFERENCES

[1]Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall G, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.

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

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

12 LIST OF APPENDICES

▪ Appendix A: Analysis Visit Windows for Safety and Efficacy Assessments

Table 12-1 Visit Window Mapping Rules

Assessments	Visit[1]	Target Study Day	Visit Window (in study days)
Safety Assessment			
• Standard 12-lead ECG • Vital signs • Pulse oximetry • Chemistry	Day 1	1	≤1 Pre-dose
	Week 2	15	[1*, 22]
	Week 4	29	(22, 43]
	Week 8	57	(43, 71]
	Safety Follow-up Visit	N/A	Nominal
• Hematology	Day 1	1	≤1 Pre-dose
	Week 2	15	[1*, 36]
	Week 8	57	[37, 71]
	Safety Follow-up Visit	N/A	Nominal
• Urinalysis • Lipid panel • Vitamin levels	Day 1	1	≤1 Pre-dose
	Week 8	57	[1*, 71]
	Safety Follow-up Visit	N/A	Nominal
• Coagulation	Day 1	1	≤1 Pre-dose
	Week 8	57	[1*, 71]
	Safety Follow-up	N/A	Nominal
Efficacy Assessment			
• Spirometry (pre-dose) • CFQ-R[a] • Weight and height	Day 1	1	≤1 Pre-dose
	Week 2	15	[1*, 22]
	Week 4	29	(22, 43]
	Week 8	57	(43, 71]
	Safety Follow-up Visit	N/A	>71
• LCI	Day 1	1	≤1 Pre-dose
	Week 2	15	[1*, 22]
	Week 4	29	(22, 43]
	Week 8	57	(43, 71]
• Sweat chloride	Day 1	1	≤1 Pre-dose
	Week 8	57	[1*, 71]
	Safety Follow-up Visit	N/A	>71
[redacted]			

* Only include day 1 post-dose measurements.
a CFQ-R is only required at the Safety Follow-up Visit for subjects who prematurely discontinue study treatment and do not have the ETT visit.
b Physical examination at Day 1, Week 8 and Safety Follow-up Visit are abbreviated ones.

Note:

1. Visit name for analysis purpose is used to report data in tables and figures.
2. The analysis visit windows will be applied for both scheduled and unscheduled visits.
3. If no measurement is available within a visit window, the assessment will be considered missing for the visit.
4. If there is more than one measurement available within the same visit window for efficacy parameters, the record at the scheduled visit will be used. Otherwise,
   - The record closest to the target day will be used.
   - If there are multiple records with the same distance to the target day, the latest record will be used.
   - Assessments at early treatment termination (ETT) visit will follow the windowing rules for regular visits up to Week 8.
   - Assessments at safety follow-up (SFU) visit will follow the windowing rules for regular visits if they fall within the upper boundary of the window for Week 8, or remain as SFU if they go beyond the upper boundary of the window for Week 8.
5. If there is more than one measurement available within the same visit window for safety parameters, then
   - The record closest to the target day will be used.
   - If there are multiple records within the same distance from the target day, the latest record will be used; or
   - SFU visit will not be windowed; instead, it will be used according to the nominal visit in relevant analyses.
6. Spirometry assessments, BMI, weight, and height will be used for [redacted] safety purpose. Their measurements will follow the visit windowing rules for efficacy parameters.
7. For post-dose spirometry, Day 1 and Week 2 will be nominal.

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

- On Day 1, the pre-dose measurements will be collected as triplets; the average of the triplicate will be used as pre-dose measurement on Day 1. Only pre-dose measurement with nominal visit names related to the triplets shall be used in this average.
- For other post-dose visits, the visit window in the above table will apply.

▪ Appendix B: Stardards for Safety and Efficacy Variable Display in TFLs

Continuous Variables

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

[redacted]

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

▪ Appendix D: Imputation Rules for Missing Prior/Concomitant Medication Dates

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date (in practical, use January 01, 2000 to impute).
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last day of the month.
    b. If DAY and Month are both missing, use the last day of the year.
    c. If DAY, Month and year are all missing, assign 'continuing' status to stop date (in practical, use December 31, 2050 to impute).

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

Table 12-2 Prior, Concomitant, and Post Categorization of a Medication

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

A: Post; C: Concomitant; P: Prior

▪ Appendix E: Imputation Rules for Missing AE dates

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

If only Day of AE start date is missing:

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

Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Day and Month of AE start date are missing:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then:
  - If the AE start year is the same as that for the first dose date, 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 day as 1.
- Otherwise, impute the AE start month as January and day as 1.

Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Year of AE start date is missing:

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

▪ Appendix F: Details of GLI Equation for Calculating ppFEV$_1$

Percent predicted values will be calculated for parameters of FEV$_1$, FVC, FEV$_1$/FVC, and FEF$_{25\%-75\%}$ using the Quanjer GLI-2012 Regression Equations and Lookup Tables.

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

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

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

Accessed Sep 11, 2017.

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

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

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

Accessed Sep 11, 2017.

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

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

Accessed Sep 11, 2017.

Data handling rule for spirometry is as follows:

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

▪ Appendix G: Criteria for Threshold Analysis

Table 12-3 Threshold Analysis Criteria for Clinical Chemistry, Hematology and Coagulation

Parameter	Threshold Criteria	Comments
LFT		
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
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
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
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
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

Non-LFT 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
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

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 – ≥ 0.6 mmol/L <0.6 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
Lipid Panel		
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
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
Coagulation		
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 12-4 Threshold Criteria for ECGs

Ref.: CPMP 1997 guideline.

Parameter	Threshold	Comments
HR	Bradycardia <50 bpm <45 bpm Decrease from baseline ≥10 bpm Decrease from baseline ≥20 bpm <50 bpm and decrease from baseline ≥10 bpm <50 bpm and decrease from baseline ≥20 bpm	Per HV grade 2, 3, plus shift change
	Tachycardia >100 bpm >115 bpm >130 bpm Increase from baseline ≥10 bpm Increase from baseline ≥20 bpm >100 bpm and increase from baseline ≥10 bpm >100 bpm and increase from baseline ≥20 bpm	Per HV grade 1, 2, 3, plus shift change

PR	≥240 ms ≥300 ms ≥200 ms and increase from baseline ≥40 ms ≥200 ms and increase from baseline ≥100 ms
QRS	>110 ms >160 ms Increase from baseline ≥20 ms Increase from baseline ≥40 ms
QTc/QTcF	>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 12-5 Threshold Criteria for Vital Signs

Parameter	Threshold Criteria	Comments
HR	Same criteria 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	CTCAE grade 1-3
	≥5 % decrease from baseline	
	≥10 % decrease from baseline	
	≥ 20% decrease from baseline	