VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX19-445-117 Version 3.0 (Final Analysis)

A Phase 3b Open-label Study to Assess the Effect of Elexacaftor/Tezacaftor/Ivacaftor on Glucose Tolerance in Cystic Fibrosis Subjects with Abnormal Glucose Metabolism

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2 MODIFICATIONS

2.1 Modifications to the Approved Clinical Study Protocol

Not Applicable.

2.2 Modifications to the Approved Statistical Analysis Plan

Not Applicable. This is the 1st version of Statistical Analysis Plan.

3 INTRODUCTION

Study VX19-445-117 is a Phase 3b open-label study evaluating the effect of elexacaftor (ELX, VX-445) in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) on glucose tolerance in cystic fibrosis (CF) subjects who are 12 years of age and older, heterozygous for *F508del* and a minimal function mutation (F/MF), and with abnormal glucose metabolism.

This statistical analysis plan (SAP) is based on the most recent approved clinical study protocol (CSP), the most recent approved electronic case report form (eCRF), and the most recent approved eCRF completion guidelines.

This SAP (Methods) version 1.0 documents the planned statistical analyses of efficacy and safety endpoints for final analysis. It also documents analyses for additional efficacy and safety variables not specified in the protocol, which will provide supportive information for the scientific understanding of the drug entity.

The Vertex Biometrics Department will perform the statistical analysis of 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 (version 1.0) will be finalized and approved prior to the clinical database lock for the study. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP.

4 STUDY OBJECTIVES

4.1 Primary Objective

To evaluate the effect of ELX/TEZ/IVA on glucose tolerance in CF subjects with impaired glucose tolerance (IGT) or CF-related diabetes (CFRD)

4.2 Secondary Objectives

To evaluate the safety and tolerability of ELX/TEZ/IVA

5 STUDY ENDPOINTS

5.1 Efficacy and Pharmacodynamic Endpoints

5.1.1 Primary Endpoint

Change from baseline in 2-hour blood glucose levels following an oral glucose tolerance test (OGTT) to the average of Week 36 and Week 48

5.1.2 Secondary Endpoint

- Proportion of subjects with improvement in dysglycemia categorization (CFRD, IGT, normal glucose tolerance [NGT]) at Week 48
- Safety and tolerability of ELX/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry

5.1.3 Other Endpoints

- Change from baseline in sweat chloride (SwCl) through Week 48
- Absolute change in body mass index (BMI) from baseline at Week 48

- Absolute change in body weight from baseline at Week 48
- Change from baseline in hemoglobin A1c (HbA1c) and fructosamine at Week 48
- Change from baseline in insulin use (dose) at Week 48 in subjects using insulin
- Change from baseline in post-OGTT diabetes-related biomarkers (including insulin, C-peptide, glucagon, calculated indices of insulin secretion [insulinogenic index], and insulin resistance [HOMA-IR]) at Week 48
- Change from baseline in biomarkers of inflammation (including C-reactive protein [CRP]) at Week 48
- Change from baseline in biomarkers of pancreatic function (including fecal elastase-1 [FE-1] and serum immunoreactive trypsinogen [IRT]) at Week 48
- Change from baseline in post-OGTT incretin levels (including glucagon-like peptide 1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]) at Week 48
- Change from baseline in percent of time spent in target blood glucose range of ≥70 to <140 mg/dL (≥3.89 to <7.77 mmol/L) as measured by 7-day continuous glucose monitoring (CGM) in subjects with CFRD at Week 48
- Change from baseline in selected CGM parameters (including but not limited to percent of time spent between ≥140 and <200 mg/dL [≥7.77 and <11.10 mmol/L], percent of time spent ≥200 mg/dL [≥11.10 mmol/L], and mean amplitude of glycemic excursion* [MAGE]) in subjects with CFRD at Week 48

*Note: definition corrected for MAGE (originally defined as maximum amplitude of glucose excursions in the study protocol).

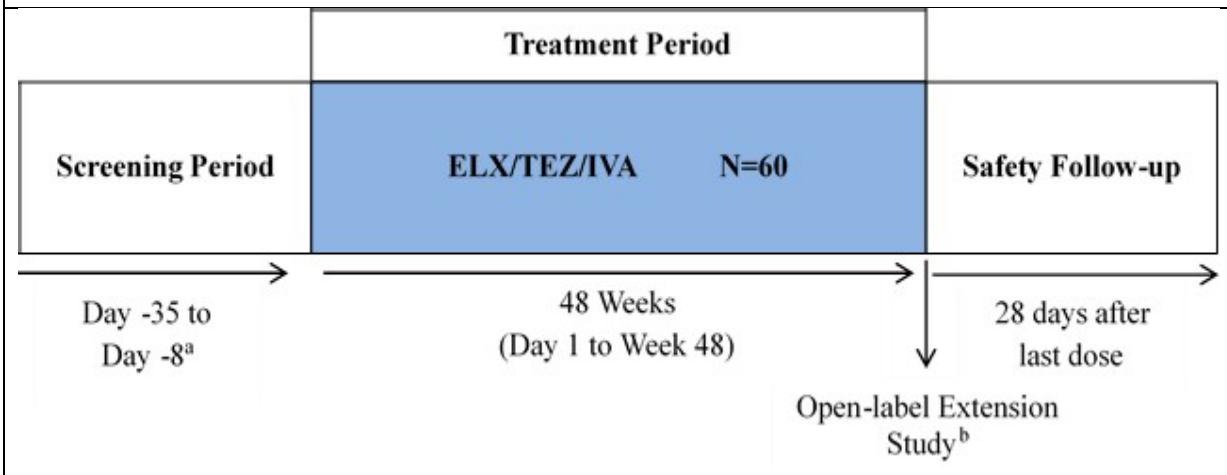
6 STUDY DESIGN

6.1 Overall Design

This is a Phase 3b, open-label study in CF subjects 12 years of age and older with F/MF genotypes and abnormal glucose tolerance as shown in Figure 7-1.

Approximately 60 subjects (F/MF genotypes) will be enrolled, of whom approximately 30 subjects will have IGT, and 30 subjects will have CFRD. During the Treatment Period, subjects will be administered ELX/TEZ/IVA for approximately 48 weeks. All subjects will receive ELX 200 mg once daily (qd)/TEZ 100 mg qd/ IVA 150 mg every 12 hours (q12h).

Figure 7-1 Schematic of the Study Design



ELX: elexacaftor; CFRD: CF-related diabetes; CGM: continuous glucose monitoring; IVA: ivacaftor; N: total sample size; TEZ: tezacaftor

[a] On Day -7, a CGM sensor will be inserted subcutaneously to assess baseline blood glucose levels for 7 days prior to the first dose of study drug in subjects with CFRD.

[b] Subjects who complete the visits in the Treatment Period, regardless of whether they are on a treatment interruption, will be offered the opportunity to enroll in an open-label extension safety study evaluating ELX/TEZ/IVA. The Safety Follow-up Visit is not required for subjects who complete the Week 48 Visit and have enrolled in an open-label study within 28 days after the last dose of study drug.

6.2 Sample Size and Power

The primary efficacy endpoint is change from baseline in 2-hour blood glucose levels following an OGTT to the average of Week 36 and Week 48. The primary null hypothesis to be tested is that the mean change from baseline in 2-hour blood glucose levels following OGTT to the average of Week 36 and Week 48 is equal to zero.

Assuming a within group standard deviation (SD) of 45 mg/dL and a 10% dropout rate at Week 48, a sample size of 60 subjects will have more than 95% power to detect a mean decrease from baseline of -30 mg/dL in 2-hour blood glucose levels post-OGTT to the average of Week 36 and Week 48, based on a 2-sided, 1-sample t-test at a significance level of 0.05.

All power calculations were based on EAST software Version 6.4.

6.3 Randomization

Not applicable.

6.4 Blinding and Unblinding

This is an open-label study. Refer to Section 10.7 of the CSP for details.

7 ANALYSIS SETS

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

7.1 All Subjects Set

The **All Subjects Set** will include all subjects who were enrolled (defined as subjects having data in the clinical database for this study). This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

7.2 Full Analysis Set

The **Full Analysis Set** (FAS) will include all enrolled subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug. The FAS will be used to summarize subject demographics and baseline characteristics, and for analyses of all efficacy endpoints, unless otherwise specified.

7.3 Safety Set

The **Safety Set** will include all subjects who have received at least 1 dose of study drug. The Safety Set is to be used for all safety analyses.

8 STATISTICAL ANALYSIS

8.1 General Considerations

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

Categorical variables will be summarized using counts and percentages.

Baseline value, unless otherwise specified, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the Treatment Period. The baseline 2-hour post-OGTT blood glucose level will be the average of pre-dose measurements at Screening and Day 1 visits (if both measurements are not available, use one measurement).

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

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

Treatment-emergent (TE) Period will include the time from the first dose of study drug to 28 days after the last dose of study drug or to the completion of study participation, whichever occurs first. Refer to Section 9.1.6 of the CSP for the definition of completion of study participation.

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

1) In scheduled visit windows per specified visit windowing rules
2) In the derivation of baseline and last on-treatment measurements
3) In the derivation of maximum and minimum values during TE period, and maximum and minimum change from baseline values during TE period for safety analyses
4) 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.

8.2 Background Characteristics

8.2.1 Subject Disposition

The number of subjects in the following categories will be summarized based on the All Subjects Set:

- All Subject Set
- FAS
- Safety Set

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

- Completed study drug treatment
- Prematurely discontinued treatment (i.e., discontinued all study drugs) and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation
- Rollover to the open-label study

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

8.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized based on the FAS.

Demographic data will include the following:

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

Baseline characteristics will include the following:

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

Disease characteristics will include the following:

- $ppFEV_1$ at baseline (<30, ≥30 to <40, ≥40 to <70, ≥70 to ≤90, and >90)
- $ppFEV_1$ at baseline (continuous)
- Sweat chloride at baseline (continuous)
- 2-hour post-OGTT blood glucose levels at baseline (continuous)
- Dysglycemia categorization at screening (IGT, CFRD)
- Insulin use at baseline (Yes, No)
- Prior use of dornase alfa (Yes, No)
- Prior use of azithromycin (Yes, No)
- Prior use of inhaled antibiotic (Yes, No)
- Prior use of bronchodilator (Yes, No)
- Prior use of inhaled bronchodilator (Yes, No)
- Prior use of inhaled hypertonic saline (Yes, No)
- Prior use of inhaled corticosteroids (Yes, No)

In addition, data listings will also be provided for:

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

The predicted FEV_1 will be calculated using the Global Lung Function Initiative (GLI); details are provided in Appendix B.

8.2.3 Medical History

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized descriptively by System Organ Class (SOC) and Preferred Term (PT) for the FAS. The corresponding data listing will also be provided.

8.2.4 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) and categorized as follows:

Prior medication: any medication that was administered during the 56 days before the first dose of study drug.

Concomitant medication: medication continued or newly received during the TE period

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

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

If a medication has a missing or partially missing start/end date or time and if it cannot be determined whether it was taken before the first dose of study drug, concomitantly during the TE

Period, or after the TE Period, it will be considered in all 3 categories of prior, concomitant, and post treatment medication. Details for imputing missing or partial start and/or stop dates of medication are described in Appendix C.

Prior medications and concomitant medications will be summarized descriptively using frequency tables by: 1) preferred name (PN); and 2) anatomic class (ATC) level 1, ATC level 2, and PN for FAS. All medications will be listed for each subject.

The number of subjects who used hormonal therapy concomitantly during the Treatment Period will be summarized based on the Safety Set.

8.2.5 Study Drug Exposure

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

Duration of study drug exposure (in weeks) will be calculated as: (last dose date of study drug – first dose date of study drug + 1)/7, regardless of study drug interruption.

Study drug exposure (in weeks) will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized by intervals, using counts and percentages.

8.2.6 Study Drug Compliance

Study drug compliance will be summarized based on the FAS.

Study drug compliance will be calculated as: 100 × [1 - (total number of days of study drug interruption) / (duration of study drug exposure in days)]. A study drug interruption on a given day is defined as an interruption of any study drugs on that day. A study drug interruption that continues through the end of the study participation (i.e., subject does not resume study drug before the end of the study participation) will not be included in the compliance calculation.

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

8.2.7 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. A protocol deviation review team will categorize IPDs according to the Protocol Deviation Plan during the study.

IPDs will be only provided in an individual subject data listing.

8.3 Efficacy Analysis

Unless otherwise defined, all efficacy analyses described in this section will be based on the FAS.

8.3.1 Analysis of Primary Efficacy Variable

8.3.1.1 Definition of Variable

The primary efficacy endpoint is change from baseline in 2-hour glucose levels following an OGTT to the average of Week 36 and Week 48.

2-hour blood glucose levels following an OGTT: OGTT will be performed to assess 2-hour glucose levels. Depending on a subject's weight, 1.75 g/kg of body weight or 75 g maximum of oral glucose solution will be administered in the morning after at least 8 hours of fasting. Blood samples will be obtained at 0, 30 (±5), 60 (±5), 90 (±5), and 120 (±5) minutes after the start of ingestion of glucose solution. OGTT results are considered valid only when the subject was fasting for at least 8 hours. Any non-fasting OGTT results will be disregarded and data for that assessment will be considered missing.

8.3.1.2 Primary Analysis

The primary analysis will be performed using a mixed-effects model for repeated measures (MMRM) with the change from baseline in 2-hour post-OGTT blood glucose levels at each post-baseline visit as the dependent variable. The model will include visit as a fixed effect, with continuous baseline 2-hour post-OGTT blood glucose level as covariate. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the *F*-test for fixed effects will be estimated using the Kenward-Roger approximation[1]. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, a compound symmetry covariance structure will be used instead. Conditional on the observed data and covariates, missing data will be assumed to be missing at random and therefore will be handled by MMRM model.

The primary result obtained from the model will be the estimated change from baseline to the average of Week 36 and Week 48. Data obtained from Week 24, Week 36, and Week 48 visits will be included in the model. The least square (LS) mean estimate along with the corresponding 2-sided 95% confidence interval (CI) and *P* value will be provided. The LS mean change from baseline at each post-baseline visit with 95% CI, obtained from the model, will also be provided. Furthermore, the LS mean change from baseline (with SE) at each post-baseline visit, obtained from the model, will be plotted.

In addition, the post-baseline raw values and the change from baseline at each post-baseline visit up to Week 48 will be summarized descriptively (n, mean, SD, median, minimum, and maximum).

8.3.2 Analysis of Secondary Efficacy Variable

8.3.2.1 Definition of Variable

Dysglycemia categorization: abnormal or normal glucose tolerance as determined by an OGTT, classified as either:

- CFRD: 2-hour post-OGTT blood glucose level ≥200 mg/dL [≥11.10 mmol/L]) or fasting hyperglycemia [blood glucose level ≥126 mg/dL (≥7.00 mmol/L) after an 8-hour fast]
- IGT: 2-hour post-OGTT blood glucose level ≥140 to <200 mg/dL [≥7.77 to <11.10 mmol/L] and fasting blood glucose level <126 mg/dL (<7.00 mmol/L)
- NGT: 2-hour post-OGTT blood glucose level <140 mg/dL [<7.77 mmol/L] and fasting blood glucose level <126 mg/dL (<7.00 mmol/L)

Improvement in dysglycemia categorization: response at Week 48 compared to baseline (i.e. CFRD at baseline to IGT or NGT at Week 48, or IGT at baseline to NGT at Week 48 OGTT).

OGTT results are considered valid only when the subject was fasting for at least 8 hours. Any non-fasting OGTT results will be disregarded and data for that assessment will be considered missing.

8.3.2.2 Analysis Method

The number and proportion of subjects with and without response at Week 48, defined as improvement from baseline dysglycemia categorization (i.e. CFRD at baseline to IGT or NGT based on Week 48 OGTT measurement, and IGT at baseline to NGT based on Week 48 OGTT measurement), will be presented for patients with abnormal glucose (CFRD or IGT) at baseline. The exact, 2-sided 95% Clopper-Pearson CI of the proportion of subjects with improvement will also be presented. In addition, the number and proportion of subjects in each dysglycemia category at baseline and each post-baseline visit will be presented.

8.3.3 Analysis of Other Variables

8.3.3.1 Definition of Variables

Sweat chloride (SwCl): the SwCl value for a given visit will be calculated as the mean of the non-missing sweat chloride measurements obtained on the left and right arms at that visit. If one of the two arm measurements at a time point is missing, the other will be used as the mean. A volume ≥15 μL is required for an accurate determination of sweat chloride. Any results reported as having volume <15 μL will be considered missing. Any sweat chloride values reported as <10 mmol/L or >160 mmol/L will be considered missing.

Body mass index (BMI): the BMI at each visit is calculated using the weight and height at each visit as follows:

$$\text{BMI} = \text{Weight (kg)} / [\text{Height (m)}]^2$$

Continuous glucose monitoring (CGM): CGM will be performed in subjects with CFRD at screening to assess dynamic, free-ranging changes in capillary glucose levels. A CGM sensor will be inserted subcutaneously by site medical staff, a home health nurse, or the subject after adequate training, calibrated, and worn for approximately 7 days. The CGM sensor records glucose values every 5 minutes.

CGM glucose values are considered valid between 39 and 401 mg/dL. Any values reported as <39 mg/dL or >401 mg/dL are considered missing. The daily CGM assessment is considered valid when at least 202 values are obtained and valid (at least 70% of 288 5-minute records). For each analysis visit, the CGM parameters will be calculated for each valid daily assessment and then averaged, provided that there are at least 4 valid daily assessments.

8.3.3.2 Analysis Method

For the following other endpoints, the raw values and change from baseline will be summarized descriptively (n, mean, SD, standard error [SE], median, minimum, and maximum):

- Change from baseline in sweat chloride (SwCl) through Week 48
- Absolute change in body mass index (BMI) from baseline at Week 48
- Absolute change in body weight from baseline at Week 48

- Change from baseline in percent of time spent in target blood glucose range of ≥70 to <140 mg/dL (≥3.89 to <7.77 mmol/L) as measured by 7-day CGM in subjects with CFRD at Week 48
- Change from baseline in percent of time spent between ≥140 and <200 mg/dL [≥7.77 and <11.10 mmol/L] and percent of time spent ≥200 mg/dL [≥11.10 mmol/L] as measured by 7-day CGM in subjects with CFRD at Week 48

The raw values and change from baseline at each post-baseline visit up to Week 48 will also be summarized descriptively (n, mean, SD, SE, median, minimum, and maximum).

8.4 Safety Analysis

All safety analyses will be based on data from the TE period based in the Safety Set, unless otherwise specified.

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
- ECGs
- Vital signs
- Pulse oximetry

Only descriptive analysis of safety will be performed, and no statistical testing will be performed.

8.4.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs, and post-treatment AEs, defined as follows:

Pretreatment AE: any AE that occurred 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 after the TE period

For AEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs are pre-treatment or TEAE, the AEs will be classified as TEAEs.

Details for imputing missing or partial start dates of adverse events are described in Appendix D.

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

- Number of TEAEs
- Subjects with any TEAEs
- Subjects with TEAEs by strongest relationship
- Subjects with TEAEs by maximum severity

- Subjects with TEAEs leading to study drug discontinuation
- Subjects with TEAEs leading to study drug interruption
- Subjects with Grade 3/4/5 TEAEs
- Subjects with related TEAEs
- Subjects with serious TEAEs
- Subjects with related serious TEAEs
- Subjects with TEAEs leading to death

The following summary tables of TEAEs will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT) using frequency counts and percentages (i.e., number and percentage of subjects with an event):

- All TEAEs
- Grade 3/4/5 TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Related TEAEs
- Serious TEAEs
- Related serious TEAEs
- TEAEs leading to death

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

All AEs, including pretreatment AEs, TEAEs, and post-treatment AEs, will be presented in an individual subject data listing based on the All Subjects Set. In addition, separate listings containing individual subject adverse event data for TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, Grade 3/4/5 TEAEs, SAEs, and all deaths will be provided. Listings for SAEs and deaths will include a flag indicating the TEAE status.

8.4.1.1 Adverse Events of Special Interest

For this study, elevated transaminase events and rash events, as determined by MedDRA preferred terms in Appendix E, are considered as adverse events of special interest.

For treatment-emergent elevated transaminase events and rash events, the following categories will be summarized by treatment group:

- Subjects with events

- Subjects with events by maximum severity
- Subjects with events leading to treatment discontinuation
- Subjects with events leading to treatment interruption
- Subjects with serious events
- Subjects with related serious events
- Subjects with events leading to death
- Duration of events
- Time-to-onset of first event

In addition, for treatment-emergent rash events, these categories will be summarized for the following subgroups:

- Sex (male, female)
- Female subjects with concomitant hormonal therapy (Yes, No)

8.4.2 Clinical Laboratory

For the treatment-emergent laboratory measurements, the observed values and change from baseline values of the continuous hematology, serum chemistry, and coagulation results will be summarized in SI units at each visit.

The number and percentage of subjects meeting the threshold analysis criterion at least once during the TE period will be summarized for select LFT parameters. The threshold analysis of shift from baseline will also be summarized for selected LFT laboratory parameters. The threshold analysis criteria are provided in Appendix F.

For selected LFT laboratory tests (alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALP], and total bilirubin), a scatter plot of the maximum treatment-emergent value versus the baseline value corresponding to ×ULN (upper limit of normal) will be presented. Further, a scatter plot of the maximum treatment-emergent value of ALT and AST, separately, versus the maximum treatment-emergent value of total bilirubin corresponding to ×ULN will also be presented.

Results of urinalysis and positive urine/serum pregnancy test will be listed in individual subject data listings only. For positive serum pregnancy listing, subjects with serum HCG which are above non-pregnant levels will be selected.

In addition, a listing containing individual subject hematology, chemistry, and coagulation values will be provided. This listing will include data from both scheduled and unscheduled visits.

8.4.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided at each visit and time point for the following ECG measurements (in msec): RR interval, PR interval, QT interval, QTcF interval, QRS duration, and Heart Rate (beats per minute).

The number and percentage of subjects meeting the threshold analysis criterion at least once during the TE period for selected parameters will be summarized. The threshold analysis criteria are provided in Appendix F.

In addition, a listing containing individual subject ECG values will be provided. This listing will include data from both scheduled and unscheduled visits.

8.4.4 Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized at each visit. The following vital signs parameters will be summarized: height (cm), systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute).

The number and percentage of subjects meeting the threshold analysis criterion at least once during the TE period for selected parameters will be summarized. The threshold analysis criteria are provided in Appendix F.

In addition, a listing containing individual subject vital signs values will be provided. This listing will include data from both scheduled and unscheduled visits.

8.4.5 Pulse Oximetry

For the treatment-emergent pulse oximetry measurements, a summary of observed values and change from baseline values will be provided at each visit for the percent of oxygen saturation.

The number and percentage of subjects with shift from baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the TE period will be summarized. The reference range for normal oxygen saturation is specified as >95%, and <=95% for low oxygen saturation.

8.4.6 Physical Examination

Abnormal PE findings will be presented as an individual subject data listing only.

8.4.7 Ophthalmology Examination

Ophthalmology examination results will be provided in a data listing.

8.4.8 COVID-19 Impacted Visits

A listing containing subjects' visits impacted due to COVID-19 will be provided.

8.5 Additional Analysis

Analyses related to the additional endpoints of change from baseline at Week 48 in hemoglobin A1c (HbA1c) and fructosamine, insulin use (dose) in subjects using insulin, post-OGTT diabetes-related biomarkers, biomarkers of inflammatory, biomarkers of pancreatic function, post-OGTT incretin levels and glucose-dependent insulinotropic polypeptide, and some selected CGM parameters (including MAGE, which was originally defined as "maximum amplitude of glucose excursions" in study protocol, but is corrected to "mean amplitude of glycemic excursion" in this SAP) will be discussed in a separate document and thus are out of the scope of this SAP.

9 Interim and DMC Analyses

9.1 Interim Analysis

Not applicable.

9.2 DMC analysis

Not applicable.

10 REFERENCES

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

11 LIST OF APPENDICES

Appendix A: Analysis Visit Windows for Safety and Efficacy Assessments

Table 11-1 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3, 4, 5]
Safety Assessment			
Serum Chemistry Hematology	Day 1 (Baseline) Week 4 Week 12 Week 24 Week 36 Week 48 Safety Follow-up	1 29 85 169 253 337 Not applicable	≤1 Pre-dose [1, 57] (57, 127] (127, 211] (211, 295] (295, 351] Use nominal visit
Standard 12-lead ECG	Day 1 (Baseline) Week 24 Week 48 Safety Follow-up	1 169 337 Not applicable	≤1 Pre-dose [1, 253] (253, 351] Use nominal visit
Vital signs (excluding BMI, Weight, and Height) and pulse oximetry	Day 1 (Baseline) Week 4 Week 12 Week 24 Week 36 Week 48 Safety Follow-up	1 29 85 169 253 337 Not applicable	≤1 [1, 57] (57, 127] (127, 211] (211, 295] (295, 351] Use nominal visit
Coagulation	Day 1 (Baseline) Week 24 Week 48 Safety Follow-up	1 169 337 Not applicable	≤1 Pre-dose [1, 253] (253, 351] Use nominal visit
Efficacy Assessment and Pharmacodynamic Assessment			
Weight, Height, and BMI	Day 1 (Baseline) Week 4 Week 12 Week 24 Week 36 Week 48 Safety Follow-up	1 29 85 169 253 337 Not applicable	≤1 (1, 57] (57, 127] (127, 211] (211, 295] (295, 351] > 351
Sweat Chloride	Day 1 (Baseline) Week 24 Week 48	1 169 337	≤1 Pre-dose (1, 253] (253, 351]
Oral glucose tolerance test (OGTT)[6]	Baseline Week 24 Week 36 Week 48	1 169 253 337	≤1 Pre-dose (1, 211] (211, 295] (295, 351]

Table 11-1 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3, 4, 5]
Continuous glucose monitoring (CGM)	Day -7 (Baseline)	-7	<1 Pre-dose
	Week 1	1	[1, 43]
	Week 12	85	(43, 127]
	Week 24	169	(127, 211]
	Week 36	253	(211, 295]
	Week 48	337	(295, 362]

Notes:

[1] Visit name for analysis purpose is used to report data in tables and figures.

[2] The analysis visit windows will be applied using the following rules for both scheduled and unscheduled visits:

a. If no numerical measurement is available within a visit window, the measurement will be considered missing for the visit.
b. If there is more than 1 numerical measurement available within a visit window, use the following rules:
   i. The measurement closest to the target day will be used; or
   ii. If there are multiple measurements with the same distance from the target day, the latest measurement will be used. If the latest measurement cannot be determined, then unscheduled visit will be selected

[3] For measurements collected on the date of first dose of study drug, if it cannot be determined whether the measurement is before or after the first dose:

a. Scheduled measurement will be treated as pre-dose observation.
b. Unscheduled measurement will be treated as post-dose observation.

[4] For safety assessment, Safety Follow-up analysis visit will be based on nominal Safety Follow-up visit. If a subject doesn't have a nominal Safety Follow-up visit but has an ETT visit with study day >351, then the ETT visit will be mapped into Safety Follow-up analysis visit.

[5] For efficacy assessments and nutrition variables (BMI, Weight, Height and their Z-scores), if there are multiple assessments >351, then nominal Safety Follow-up visit will be mapped to Safety Follow-up visit. If there is only ETT assessment > 351, the ETT visit will be mapped to the Safety Follow-up visit; else if there are multiple assessments with >351 then select the earliest record.

Derived Variables:

1. Age (in years) at first dose date and nominal visit (for demographics, listing and the calculation of [percent] predicted spirometry variables):

   Obtain the age at informed consent (in days) in "yy, mm" format (e.g., 24 years, 6 months) from the Vital Signs (VS) page at the Screening Visit, and add 0.5 month to convert to days.

   Obtain the informed consent date.

   Then age (in years) at first dose or nominal visit = [(first dose date or nominal visit date – informed consent date) in days + age at informed consent (in days)]/365.25.

2. Age (in months) at nominal visit (for use in calculation of BMI, height and weight z-score):

   Obtain the age at informed consent (in months) in "yy, mm" format (e.g., 24 years, 6 months) from Vital Signs (VS) page at the Screening Visit.

   Obtain the informed consent date.

Table 11-1 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3, 4, 5]

Then age (in months) at nominal visit = integer part of {[(age at informed consent (in months) + 0.5 + diff(first dose date or nominal visit date, informed consent date) in months]} + 0.5.

3. Missing first dose date or last dose date

   If the first dose date is missing, use Day 1 visit date to impute.

   If the last dose date is missing or partial date is reported, the last dose date will be imputed based on, in descending order priority, the Early Treatment Termination (ETT) visit date, last visit date before the Safety Follow-up, or the last study drug administration date from EX SDTM domain, as appropriate. The imputation algorithm will ensure the imputed last dose date does not exceed the study participation end date.

4. Sweat Chloride:

   Non-missing sweat chloride concentrations from the left arm and right arm with assessment end date/time for a given arm up to 30 minutes after first dose time in treatment period will be considered for baseline.

5. Electrocardiogram:

   Baseline is defined as the most recent pretreatment measurement before the first dose of study drug in the Treatment Period. If multiple ECG measurements are obtained on the same calendar day during the TE period,

   - For summary purpose, the calculated average ECG will be used as the ECG value on that day;
   - For threshold analysis purpose, all reported ECG values will be used.

[6] For the primary endpoint, the baseline 2-hour post-OGTT blood glucose level will be the average of pre-dose measurements at Screening and Day 1 visits (if both measurements are not available, use one measurement). For the secondary endpoint, the baseline dysglycemia category will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the Treatment Period.

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

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

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

Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Quanjer GLI-2012 Regression Equation and Lookup Tables (Version 7 April 2013). Global Lung Function Initiative. [online] Available at: http://www.ers-education.org/home/browse-all-content.aspx?idParent=138978 [Accessed Mar 26, 2018].

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

Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Implementing GLI-2012 regression equations (Version 19 July 2015). Global Lung Function Initiative. [online] Available at: http://www.ers-education.org/home/browse-all-content.aspx?idParent=138979 [Accessed Mar 26, 2018].

Sanja Stanojevic. GLI-2012 - SAS Macro (Version 2, 7 April 2013). Global Lung Function Initiative. [online] Available at: http://www.ers-education.org/home/browse-all-content.aspx?idParent=138988 [Accessed Mar 26, 2018].

Data handling rule for spirometry is as follows:

- Input age with at least 2 decimal place
- Use height at screening regardless if height is collected at other study visits for subjects whose age at informed consent is >21 years. For subjects with age <=21 years, height collected at the respective visit should be used; if the height at the respective visit is not available, the last non-missing record will be used.
- For race, map the CRF reported Black or African American to Black, all other races in CRF (except White) are mapped to 'other'; multiple checks for race in CRF are also mapped to 'other'; white is a reference race in the equations and assumes 0 values for all race coefficients in the GLI equations.

Appendix C: 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 (to impute in practical, use the informed consent/assent date 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 the End of Study Date to impute).

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

	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	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

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

Appendix D: Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined below. If the imputed AE start date is before the informed consent date, the AE start date will be imputed using the study informed consent date.

- **If only Day of AE start date is missing:**
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then
        - if AE start year and month are equal to the month and year of first dose date of the Treatment Period, then impute the AE start day as the day of first dose date of the Treatment Period;
        - else impute the AE start day as 1.
    - else 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 of the Treatment Period or AE end date is missing, then
        - if AE start year is equal to the year of first dose date of the Treatment Period, then impute the AE start month and day as the month and day of first dose date of the Treatment Period;
        - else impute the AE start month as January and day as 1.
    - else 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 and
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then impute the AE start date as the first dose date of the Treatment Period;
    - else impute the AE start date as the informed consent/assent date.

Imputation rules for partial AE end date are defined below:

- Impute the AE end date as min (the last day of the month, end of study participation) if day is missing, or min (Dec, end of study participation) if month is missing.

Appendix E: Adverse Events of Special Interest

Table 11-7 MedDRA Preferred Terms for Event of Special Interest

Adverse event of special interest	MedDRA preferred terms
Elevated transaminases	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
Rash	Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash vesicular, Rash pruritic, Rash follicular, Rash pustular, Nodular rash, Drug eruption, Fixed eruption, Urticaria, Urticaria papular, Urticaria vesiculosa, Urticarial dermatitis, Rash morbilliform, Rash papular, Rash papulosquamous, Rash rubelliform, Rash scarlatiniform , Drug hypersensitivity, Type IV hypersensitivity reaction, Dermatitis, Dermatitis atopic, Epidermolysis, Skin toxicity, Dermatitis allergic, Dermatitis exfoliative, Dermatitis exfoliative generalised, Erythema multiforme, Exfoliative rash, Mucocutaneous rash, Acute generalised exanthematous pustulosis, Cutaneous vasculitis, Urticarial vasculitis, Dermatitis bullous, Drug reaction with eosinophilia and systemic symptoms, Epidermal necrosis, Oculomucocutaneous syndrome, Skin exfoliation, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, Perioral dermatitis, Vasculitic rash, Immune-mediated dermatitis, Penile rash, SJS-TEN overlap, Erythrodermic atopic dermatitis, Scrotal dermatitis, Anal Rash, generalised bullous fixed drug eruption, Severe cutaneous adverse reaction

Note: the preferred terms listed in the table is based on the MedDRA version applicable at the time of finalization of the SAP. If the MedDRA version is upgraded at the time of the analysis, the corresponding preferred terms based on the upgraded version, including adding, removing and renaming the preferred terms, will be used in the analysis of adverse events of special interest.

Appendix F: Criteria for Threshold Analysis

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

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

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

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

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

Parameter	Threshold Analysis	Comments
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
	Platelet increased >ULN	No CTCAE available
Reticulocytes/Erythrocytes (%)	<LLN >ULN	No CTCAE
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 Analysis Criteria for ECGs

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

Table 12-4 Threshold Analysis Criteria for ECGs

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

Table 12-5 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
Pulse Rate	Same as above in ECG category	
SBP increased	>140 mmHg >160 mmHg >10 mmHg increase from baseline >20 mmHg increase from baseline >140 mmHg & >10 mmHg increase from baseline >140 mmHg & >20 mmHg increase from baseline >160 mmHg & >10 mmHg increase from baseline >160 mmHg & >20 mmHg increase from baseline	809/770 analyses
SBP decrease	<90 mmHg <80 mmHg >10 mmHg decrease from baseline >20 mmHg decrease from baseline <90 mmHg and >10 mmHg decrease from baseline <90 mmHg and >20 mmHg decrease from baseline <80 mmHg and >10 mmHg decrease from baseline <80 mmHg and >20 mmHg decrease from baseline	Per HV grade 1, 3, plus shift change

Table 12- Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
DBP increased	>90 mmHg >100 mmHg >5 mmHg increase from baseline >10 mmHg increase from baseline >90 mmHg and >5 mmHg increase from baseline >90 mmHg and >10 mmHg increase from baseline >100 mmHg and >5 mmHg increase from baseline >100 mmHg and >10 mmHg increase from baseline	
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 ≥5 % increase from baseline ≥10 % increase from baseline ≥ 20% increase from baseline	CTCAE grade 1-3
	Weight loss ≥5 % decrease from baseline ≥10 % decrease from baseline ≥ 20% decrease from baseline	CTCAE grade 1-3

Table 11-6 Threshold Analysis Criteria for Laboratory Tests (for labeling purpose)

Parameter	Threshold Analysis	Comments
Clinical Chemistry (LFT)		
ALT or AST	>3xULN >5xULN >8xULN	For labeling purpose