Statistical Analysis Plan

Vertex Pharmaceuticals Incorporated

Protocol: CP656.2001

Treatment: CTP-656

A Phase 2, Randomized, Parallel-Group, Double-Blind, Placebo Controlled Study to Evaluate the Safety and Efficacy of CTP-656 with an Open-Label Active Comparator in Patients with Cystic Fibrosis with CFTR Gating Mutations

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Contents

ABBREVIATIONS **5**

1 INTRODUCTION **6**

2 STUDY OBJECTIVES **7**

2.1 EFFICACY ENDPOINTS 7
2.2 SAFETY ENDPOINTS 7

3 STUDY DESIGN **7**

3.1 DISCUSSION OF STUDY DESIGN 7
3.2 STUDY TREATMENT 8
3.3 STUDY SCHEDULE 8
3.4 STUDY RESTRICTIONS AND PROHIBITIONS 10
3.5 ANALYSIS POPULATIONS 10
3.5.1 All Randomized Patients *10*
3.5.2 Full Analysis Population Set (FAS) *10*
3.5.3 Safety Population *10*
3.6 PATIENT STUDY AND TREATMENT DISCONTINUATION 10
3.7 RANDOMISATION 11
3.8 BLINDING 11
3.9 SAMPLE SIZE 11

4 STATISTICAL METHODOLOGY **12**

4.1 PLANNED ANALYSES 12
4.2 INTERIM ANALYSIS 12
4.3 TIME POINT ALGORITHMS 12
4.3.1 Relative Day *12*
4.3.2 Windows *12*
4.4 PATIENT DISPOSITION 13
4.5 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS 13
4.6 TREATMENT EXPOSURE AND COMPLIANCE 14
4.7 PRIOR AND CONCOMITANT MEDICATIONS 14
4.8 EFFICACY ANALYSIS 15
4.8.1 Sweat Chloride *15*
4.8.2 Percent Predicted FEV_1 ..... *15*
4.8.3 Cystic Fibrosis Questionnaire-Revised (CFQ-R) *15*
4.9 SAFETY ANALYSIS 16
4.9.1 Adverse events *16*
4.9.1.1 Adverse Event Severity 16
4.9.1.2 Relationship of Adverse Events to Study Drug 17
4.9.1.3 Serious Adverse Events 17
4.9.1.4 Treatment-Emergent Adverse Events 17
4.9.2 Clinical Laboratory Assessments *18*
4.9.3 Vital Signs *18*
4.9.4 12-Lead ECG *18*
4.10 PROTOCOL VIOLATIONS OR DEVIATIONS 18
4.11 MISSING VALUES – MISSING VISITS 18
4.12 DEVIATIONS FROM SAP 18
4.13 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL 19

5 TABLES AND LISTINGS 20
5.1 TABLE FORMAT 20
5.2 CONVENTIONS 20
6 LIST OF TABLES, FIGURES AND LISTINGS 22
7 REFERENCES 24
9 APPENDICES 25
APPENDIX A. CYTOCHROME P450 DRUG INTERACTIONS 25
[redacted]
APPENDIX D. LABORATORY ASSESSMENTS 31
APPENDIX E. THRESHOLD ANALYSIS CRITERIA 32

Abbreviations

Abbreviation or special term	Explanation
AE	adverse event
ATC	Anatomical-Therapeutic-Chemical
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFR	Code of Federal Regulations
CFTR	cystic fibrosis transmembrane conductance regulator
CRF/eCRF	case report form/electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTP-656	D9-ivacaftor
DMC	Data Monitoring Committee
ECG	Electrocardiogram
FAS	Full Analysis Set
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
FEF_{25-75}	forced expiratory flow over the middle half of the forced vital capacity
G551D	a missense mutation that results in the replacement of a glycine residue at position 551 of the CFTR with an aspartic acid residue
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
MedDRA	Medical Dictionary for Regulatory Activities
OC	observed cases
PK	pharmacokinetic(s)
PT	preferred term
QTcF	Fridericia-corrected QT interval
SAE	serious adverse event
SOC	system organ class
TEAE	treatment emergent adverse event
WHO	World Health Organization

1 Introduction

This document presents the statistical analysis plan (SAP) for Vertex Pharmaceuticals Incorporated Protocol CP656.2001: A Phase 2, Randomized, Parallel-Group, Double-Blind, Placebo Controlled Study to Evaluate the Safety and Efficacy of CTP-656 with an Open-Label Active Comparator in Patients with Cystic Fibrosis with CFTR Gating Mutations. The study was terminated by Vertex Pharmaceuticals Incorporated on July 27, 2017 and a total of 11 subjects were treated.

Cystic fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality. Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that results in absent or deficient function of the CFTR protein at the cell surface.

Kalydeco® (ivacaftor), is the first targeted therapeutic agent for the treatment of CF in patients with the G551D CFTR mutation. Ivacaftor potentiates the function of the mutant CFTR chloride channel present on the apical surface of bronchial epithelial cells. Ivacaftor is extensively metabolized in humans and is dosed twice-daily. CTP-656 is a deuterated isotopolog of ivacaftor that has demonstrated a reduced rate of clearance, increased exposure, greater plasma levels at 24 hours, and longer half-life compared to Kalydeco in Phase 1 studies in healthy volunteers, enabling once daily dosing in the clinical setting.

This analysis plan is based on the protocol amendment #1 dated 24OCT2016.

The SAP provides the description of the analysis for the final safety and efficacy analyses.

2 Study Objectives

The objectives of this study are to evaluate the efficacy and safety of CTP-656 in patients with cystic fibrosis (CF) who have one of the following cystic fibrosis transmembrane conductance regulator (CFTR) gating mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R, and have been stable for at least 3 months on Kalydeco therapy prior to screening.

2.1 Efficacy Endpoints

Primary Endpoint

- Change from baseline in sweat chloride at Day 28

Secondary Endpoints

- Change from baseline in percent predicted FEV_1 at Day 28
- Change from baseline in CFQ-R Respiratory Domain at Day 28

[redacted]

2.2 Safety Endpoints

- Adverse Events
- Prior and Concomitant Medications
- Vital Signs
- Electrocardiograms (ECGs)
- Clinical Laboratory Tests

3 Study Design

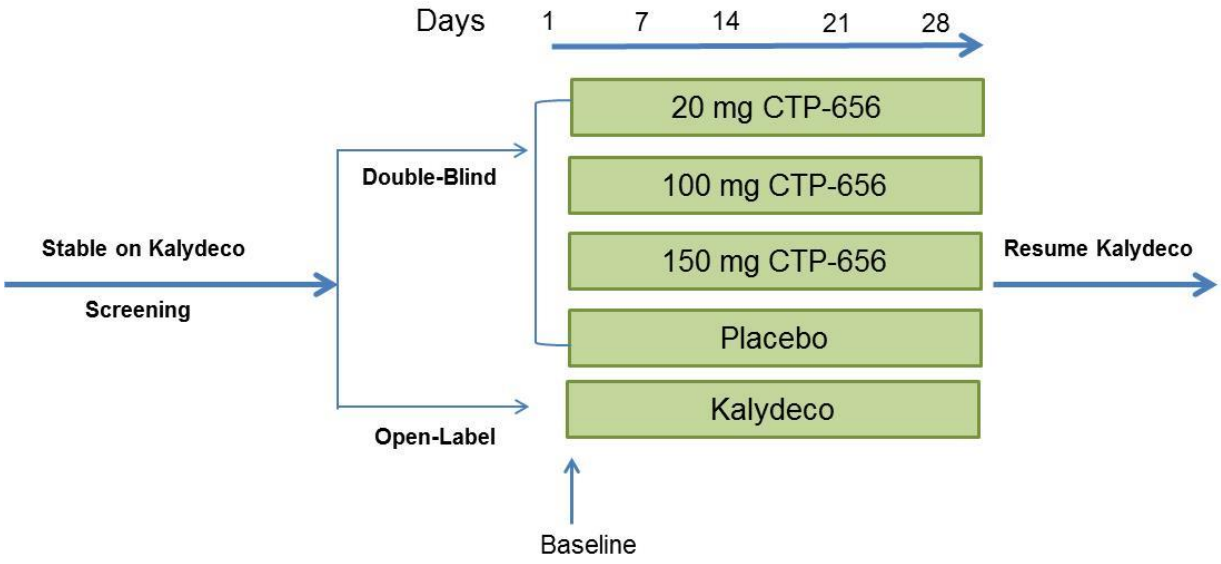
3.1 Discussion of Study Design

This is a randomized, parallel-group, double-blind, placebo controlled multicenter study in approximately 30-40 patients with CF who have a CFTR gating mutation (G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R). The study will include an open-label active comparator, i.e., Kalydeco. Patients will be ≥ 18 years old, have been stable for 3 months on Kalydeco therapy prior to the screening, and have percent predicted $FEV_1 \geq 60\%$ predicted for age, sex and height. Following screening, patients meeting all inclusion and no exclusion criteria will be randomized (1:1:1:1:1), utilizing an Interactive Response System (IXRS), to one of the 5 treatment groups shown below:

- Double-blinded CTP-656 20 mg for 28 days

- Double-blinded CTP-656 100 mg for 28 days
- Double-blinded CTP-656 150 mg for 28 days
- Double-blinded Placebo for 28 days
- Remain on (open-label) Kalydeco for 28 days

Figure 1



3.2 Study Treatment

CTP-656 (20 mg, 100 mg or 150 mg) or Placebo will be administered orally once-daily after consumption of a small meal. Patients in the open-label Kalydeco group will be instructed to continue taking Kalydeco after consumption of fat-containing food as prescribed.

Table 1: CTP-656 and Placebo Administration Schedule

Treatment Group	**Dose Unit**	**Dose**
CTP-656 20 mg	20 mg	1 x CTP-656 tablet (20 mg) + 1 x Placebo tablet
CTP-656 100 mg	100 mg	1 x CTP-656 tablet (100 mg) + 1 x Placebo tablet
CTP-656 150 mg	75 mg	2 x CTP-656 tablets (75 mg)
Placebo	Not applicable	2 x Placebo tablets

3.3 Study Schedule

Schedule of assessments are presented in Table 2 as follows.

Table 2: Schedule of Events

Event	Screening	Study Treatment						Follow-up
	Visit 1 Day - 14 to Day -1	Visit 2 Day 1	Day 3±1	Visit 3 Day 7±1	Visit 4 Day 14±1	Day 21±1	Visit 5 (or ET) Day 28[10]	Visit 6 Day 35±1
Informed consent	X							
Randomization		X						
Eligibility assessment[1]	X	X						
Demographics	X							
Medical history[2]	X	X						
Physical examination[3]	X	X		X	X		X (full physical for ET)	X
Height (cm)	X							
Weight	X	X		X	X		X	X
Pregnancy test[4]	X	X					X	X
Clinical laboratories[5]	X	X					X	X
LFTs	X	X			X		X	
HbsAg, and HCV antibodies	X							
Urinalysis	X						X	
12-lead ECG	X	X		X	X		X	X
Vital signs	X	X		X	X		X	X
Sweat chloride assessment		X		X	X		X (not for ET)	
Spirometry (FEV_1 assessment)	X	X		X	X		X	
CFQ-R		X					X	
Dispense study treatment[6] (CTP-656 or Placebo)		X		X	X			
Study treatment accountability (for CTP-656 and Placebo)				X	X		X	
Blood/plasma collection for PK[7] (excluding open-label Kalydeco)		X			X		X (not for ET)	
Phone-call			X[8]			X[8]		
Adverse events	Ongoing (including screening visit)							
Prior and concomitant medications	X[9]							

CFQ-R = Cystic Fibrosis Questionnaire-Revised; LFTs = liver function tests; ECG = electrocardiogram; ET = early termination; FEV_1 = Forced expiratory volume in 1 second; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; PK = pharmacokinetics

[1] Eligibility assessment will include CF mutation genotype confirmation via medical record; FEV_1 assessment will be the only eligibility assessment conducted on Day 1 [2] Medical history will include history of alcohol and illicit drug use and HIV infection [3] Full physical examination will be performed at screening, Visit 5 (if ET), and Visit 6; symptom-directed physical examinations will be performed at other visits [4] Pregnancy tests are required for women of childbearing potential [5] Clinical chemistry, hematology, and coagulation: to be conducted prior to administration of dose on Day 1 and after the last dose on Day 27 or Day 28 [6] Applicable only to patients randomized to the double-blind CTP-656 or Placebo groups [7] Blood samples will be collected pre-dose and 1 time point each within the following 2 time windows postdose: (1) between 30 minutes and 2 hours postdose and (2) between 4 and 6 hours post-dose on Visit 2, Visit 4 and Visit 5; At Visit 5, the predose sample should be taken at 24±4 hours from the previous/last dose [8] On Day 3 and Day 21, the patient will receive a phone call or text message to discuss any adverse events or other medical changes [9] Patients who are prescribed inhaled cycling antibiotics should start Day 1 of the 28-day cycle on Day 1 of CTP-656 or Placebo treatment [10] Day 28 visit can occur on Day 27 or Day 28

3.4 Study Restrictions and Prohibitions

The medications permitted during the study will be those that the patients have been taking as part of their stable CF background therapy regimen, excluding specific prohibited concomitant medications, and those that may be necessary for the treatment of an AE, in the opinion of the Investigator. The use of concomitant medication must be documented in the patient's eCRF and in the source documents. Prohibited concomitant medications are the substances known to be substrates that induce or inhibit CYP3A (Appendix A). These compounds must not have been taken within 30 days of Day 1 and may not be administered as a concomitant medication.

3.5 Analysis Populations

3.5.1 All Randomized Patients

All randomized patients includes all patients who are randomized into this study. Patients will be grouped by the treatment to which they are assigned at randomization. All listings except screen failure will use All Randomized Patients.

3.5.2 Full Analysis Population Set (FAS)

Patients who receive at least one dose of study treatment and have at least one post-baseline measurement of sweat chloride will be included in the Full Analysis Population Set (FAS). Patients will be grouped by the treatment to which they are assigned at randomization. Efficacy analyses will be based on the FAS population.

3.5.3 Safety Population

The Safety Population will include all randomized patients who receive at least one dose of study treatment. In the unlikely event that errors may have occurred that the randomized treatment is different from the treatment received, analyses using the Safety Population will be based on treatment actually received. This population will be used for baseline characteristics and for safety data summaries.

3.6 Patient Study and Treatment Discontinuation

All patients are free to withdraw from participation in the study at any time, for any reason, and without prejudice. The Investigator must withdraw any patient from the study if the patient requests to stop participating in the study. The Investigator, Sponsor, or its designee may remove a patient from the study at any time and for any reason. The specific reason for the withdrawal should be carefully documented on the eCRF.

Patients who withdraw consent from the study prior to Day 28 will be asked if they are willing to return to the clinic for an early-termination evaluation.

A patient who prematurely discontinues study treatment should have early termination safety, spirometry and CFQ-R assessments performed (Refer to Table 2) and will be followed, as applicable.

Patients who withdraw or are withdrawn from the study may not be replaced.

3.7 Randomisation

Patients will be randomized in (1:1:1:1:1) ratio to one of the 5 treatment groups: Double blinded CTP-656 20 mg, Double-blinded CTP-656 100 mg, Double-blinded CTP-656 150 mg, Double-blinded Placebo, and continuing Open-label Kalydeco.

3.8 Blinding

Randomization schedule should be kept in blind status for the 4 double-blinded treatment groups during the entire study duration, to patients, investigator and all project team members, except if unblinding is needed due to an adverse event. Only after database lock, randomization schedule could be unblinded based on Sponsor approval.

3.9 Sample Size

Estimates for the standard deviation of change from baseline in sweat chloride were obtained from 4 sources[1,2,3,4]. Reported values ranged from 10 to 14 mmol/L, and a value of 15 mmol/L was assumed for sample size calculations in order to reduce the likelihood of overestimating power. [redacted] A sample size of 6 subjects per group will provide 87% power for a 2-sided, unpaired t-test with 0.05 Type I error under these assumptions.

4 Statistical Methodology

4.1 Planned Analyses

- Efficacy assessments (sweat chloride, percent predicted FEV_1, and CFQ-R domains) will be summarized by treatment group and visit in the FAS population according to the randomized treatment.
- Demographic/baseline characteristic and safety data will be summarized by treatment group with descriptive statistics in the Safety population according to the actually received treatment.
- All data will be reported in data listings.

Unless otherwise specified, baseline is defined as the last assessment performed prior to or on the date of first dose of study treatment (Day 1).

4.2 Interim Analysis

An interim analysis for Data Monitoring Committee (DMC) review will be performed upon completion of 3 patients per treatment group through Day 14. A separate DMC SAP describing the DMC data analysis has been finalized.

4.3 Time Point Algorithms

4.3.1 Relative Day

First study treatment dose will be administered on Day 1. The day of first dose of study treatment is considered as Day 1 and the day before the first dose of study treatment will be relative Day -1. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days):

$$\text{Relative day} = \begin{cases} \text{Date of assessment} - \text{Date of start of study treatment} \\ \text{for assessments before start of study treatment} \\ \\ \text{Date of assessment} - \text{Date of start of study treatment} + 1 \\ \text{for assessments on or after start of study treatment} \end{cases}$$

4.3.2 Windows

Data will be summarized, analyzed and reported as per the study visit as recorded on the electronic case report form (eCRF), even if the assessment is outside of the protocol-defined visit window. No windowing of visits will be performed for data tabulations. Data collected at unscheduled visits will be included in patient listings, but will not be assigned to a scheduled visit for data summaries.

4.4 Patient Disposition

Disposition status (completed or discontinued the study and treatment), including reason for discontinuation, date of last dose, and date of study completion/discontinuation, will be presented. The following will be summarized for all randomized patients:

- The number of patients randomized
- The number of patients randomized but not dosed (if applicable)
- The number and percentage of patients in the Safety population
- The number and percentage of patients in the FAS population
- The number and percentage of patients who completed study treatment
- The number and percentage of patients who prematurely discontinued study treatment and the reason for discontinuation
- The number and percentage of patients who completed study
- The number and percentage of patients who prematurely discontinued study and the reason for discontinuation

A listing including all disposition status data will be generated for all randomized patients. A separate listing will include the randomization number, date of randomization, randomized treatment and the population flags for all randomized patients.

A listing of screen failures will also be produced.

4.5 Demographics and Other Baseline Characteristics

Demographics

Age will be calculated as (Informed consent date – date of birth + 1)/365.25 and presented to 1 decimal place. No rounding will be carried out prior to summarizing age.

Body Mass Index (BMI) will be calculated as: Weight (kg) / [Height (m)]^2.

Sex, race, ethnicity, CF genotype, and categorized baseline percent predicted FEV_1 (60%-90%, and above 90%) will be summarized using counts and percentages. Age, baseline percent predicted FEV_1, baseline height (cm), baseline weight (kg), and baseline BMI (kg/m^2) will be summarized with descriptive statistics (number of patients [n], mean, standard deviation [SD], median, minimum [min], and maximum [max]). Summaries will be generated for the Safety population. A corresponding listing will be generated.

Medical History

Medical history will be recorded at Screening. Medical history data will include any prior reaction to drugs, use of alcohol and tobacco, history and treatment (if any) of cardiovascular, pulmonary, gastrointestinal, hepatic, renal, immunologic, neurologic, or psychiatric diseases, and confirmation of relevant inclusion criteria. Medical history data will be coded with the Medical Dictionary for Regulatory Activities (MedDRA v19.1) and summarized using frequency tabulations by system organ class and preferred term. The incidence is only one occurrence of a system organ class/preferred term per subject. If a subject reports multiple medical histories under the same system organ class or preferred term, then the count of incidences for that system organ class or preferred term will only be incremented by one.

Medical history information will be displayed in a patient listing.

4.6 Treatment Exposure and Compliance

Exposure to study drug (i.e., duration of treatment) of the 4 blinded treatments will be summarized in terms of the duration of subject treatment (in days). Duration of treatment, defined as Date of last dose – Date of first dose + 1, will be summarized using descriptive statistics. Study drug exposure with the relevant information will be presented in an individual subject data listing for all randomized subjects. Exposure summaries will be based on the Safety Population.

For the 4 blinded treatments, number of tablets dispensed, number of tablets returned, missed doses, and tablets unaccounted for (lost) will be recorded in the eCRF at study visits Day 1, Day 7, Day 14, and Day 28. Number of tablets taken for a patient is calculated as:

$$Tablets\ dispensed - Tablets\ returned - Tablets\ unaccounted$$

As each patient would take 2 tablets once daily for 28 days per protocol, number of tables planned for a patient is expected to be 56.

Patient treatment compliance (percentage) is calculated using number of tablets taken and number of tablets planned, compliance percentage = number of tablets taken / 56 × 100%.

Compliance data will be presented in a listing for all randomized patients. Treatment compliance will be summarized using descriptive statistics and presented in a table for the FAS population.

4.7 Prior and Concomitant Medications

All prior medications taken within 30 days prior to screening and concomitant medications taken during the study after the first study drug administration will be recorded. The World Health Organization (WHO) Drug Dictionary March 2016 will be used to code prior and concomitant medications. The WHO Anatomical-Therapeutic-Chemical (ATC) classification and preferred drug name will be attached to the clinical database.

Prior medications are defined as any medication given prior to and stopped before the subject receives the first dose of study medication. Concomitant medications are defined as any medication given to the subject starting on or after the day the subject received the first dose of study medication or given prior to the subject receiving the first dose of study medication and continuing to receive it during the study.

If the start date of medication is unknown, then the medication will be considered:

- Prior to study medication if the end date is prior to the subject receiving the first dose of study medication
- Concomitant with study medication if the end date is either on or after the first dose of study medication, if the end date is unknown, or if the medication is ongoing.

If both the start and end dates are unknown, then the medication will be considered concomitant.

Prior and concomitant medications will be summarized by ATC classification and preferred name.

A detailed listing will be produced for prior/concomitant medications with a yes/no flag for prior medications.

4.8 Efficacy Analysis

Efficacy endpoints will be graphically displayed for each individual subject in a Swimmer's plot. Subjects in different treatment group will use different symbol scheme to distinguish from each other.

[redacted]

4.8.1 Sweat Chloride

Sweat chloride is measured at Visit 2/Day 1, Visit 3/Day 7, Visit 4/Day 14, and Visit 5/Day 28 Change from baseline at [redacted] Day 28 in sweat chloride will be graphically displayed in a Swimmer's plot for each individual subject.

Sweat chloride data will be presented in a listing.

Given sweat chloride data would be potentially unblinding, dummy data will be generated for producing blinded statistical output before study unblinding.

4.8.2 Percent Predicted FEV_1

FEV_1 is assessed using spirometry at Visit 1/Screening, Visit 2/Day 1, Visit 3/Day 7, Visit 4/Day 14, and Visit 5/Day 28. For percent predicted FEV_1, recorded as "FEV1 Best (% predicted)" in eCRF, Change from baseline (Day 1) at [redacted] Day 28 in percent predicted FEV_1 will be graphically displayed in a Swimmer's plot for each individual subject.

Spirometry data, including FEV_1 Best (liter), FEV_1 2nd Best (liter), FEV_1 Best (% predicted), FVC Best (liter), FVC 2nd Best (liter), FVC Best (% predicted), FEF_{25-75} Best (liter/second), FEF_{25-75} 2nd Best (liter/second), and FEF_{25-75} Best (% predicted), will be presented in a listing.

4.8.3 Cystic Fibrosis Questionnaire-Revised (CFQ-R)

CFQ-R assessments are performed at Visit 2/Day 1 and Visit 5/Day 28. [redacted] The questionnaire consists of 12 domains: physical, vitality, emotion, eating, treatment burden, health perceptions, social, body image, role, weight, respiratory, and digestion. [redacted] Values for each question range from 1 to 4 [redacted] For questions listed horizontally (left to right) the left response category should be assigned a value of 1, the second category should be assigned a 2, the third a 3, and the rightmost category should be assigned a 4. For questions that are listed vertically (top to bottom), the top category should be assigned a value of 1, the next a 2, the third a 3, and the bottom category a 4. Some of the questions [redacted] are phrased in a positive direction [redacted] and the score for each of these questions will be reversed as: 1 = 4, 2 = 3, 3 = 2, 4 = 1, 5 =5.

The scaled score for each domain is calculated using the formula below:

$$Scaled\ Score = \frac{Sum\ of\ responses - Minimal\ possible\ sum\ (n \times 1)}{Maximum\ possible\ sum\ (n \times 4) - Minimal\ possible\ sum\ (n \times 1)} \times 100$$

Where n is the number of items within the domain.

If the respondent is missing more than half of the items within a domain, the domain scale will not be calculated. If the patient is missing half or less of the domain items at a specific

assessment, the missing values will be replaced by the mean of the other recorded responses in that domain.

[redacted]

Change from baseline in CFQ-R respiratory scale at Day 28 will be graphically displayed in a plot for each individual subject.

CFQ-R individual item scores and calculated scale scores for each of the 12 domains will be presented in a listing.

4.9 Safety Analysis

4.9.1 Adverse events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (using MedDRA v19.1).

Adverse events will be classified as pretreatment AEs or treatment-emergent AEs (TEAEs).

Pre-treatment AEs will be defined as AEs that are reported or worsened after signing the informed consent form and prior to date of first study drug dose.

TEAEs will be defined as AEs that occur post first study drug dose or AEs noted prior to the first study drug administration that worsen after Baseline. Adverse events will be considered treatment emergent if the onset date is on or after the date of first dose study drug and on or prior to the date of last dose study drug + 28 days. Only TEAEs will be summarized in tables.

Adverse event summary tables will include Overall summary of AEs (counts, percentage of patients, number of total events) for: (1) all Pre-treatment AEs (2) all TEAEs (3) treatment-related TEAEs (4) treatment-emergent SAEs (5) TEAEs leading to study drug discontinuation (6) TEAEs of Grade 3 or higher severity (7) TEAEs by maximum severity

Frequency tables will be presented by treatment group for TEAEs listed in the table of overall summary of AEs by system organ class and preferred term for number of events, number of patients, and percentage of patients. The patient level incidence is only one occurrence of a preferred term/system organ class per patient. That is, if a patient reports multiple AEs under the same preferred term, then the count of patient level incidences for that preferred term will only be incremented by one. If a patient reports multiple AEs under the same system organ class, then the count of patient level incidences for that system organ class will also only be incremented by one.

In addition, a frequency table will be presented by treatment group for all TEAEs by system organ class and preferred term for number of events, number of patients, and percentage of patients by maximum severity and study drug relationship.

4.9.1.1 Adverse Event Severity

Severity of AEs will be graded on a 5 point scale: mild = grade 1, moderate = grade 2, severe = grade 3, life-threatening = grade 4, and death = grade 5, according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The severity grade of events for which the investigator did not record severity will be categorized as “Missing” for tabular summaries and data listings, and will be considered the least severe for the purposes of

sorting for data presentation. For summaries by severity grade, if a subject has multiple events occurring in the same SOC or PT, then the most severe event will be presented.

4.9.1.2 Relationship of Adverse Events to Study Drug

Causal relationship of AE with the study drug will be classified by the investigator as "definitely related", "probably related", "possibly related", "unlikely related", and "not related". All AEs with relationship to study drug of "definitely related", "probably related", or "possibly related" will be defined as related to study drug. All AEs with relationship to study drug of "unlikely related" or "not related" will be defined as unrelated to study drug. Events for which the investigator did not record relationship to study drug will be considered related to study drug for tabular summaries. Data listings will show the relationship as missing for such events.

4.9.1.3 Serious Adverse Events

A serious adverse event (SAE) is any AE during this study that results in one of the following outcomes:

- Is fatal (results in death)
- Is life-threatening (Note: the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that could hypothetically have caused death had it been more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay)
- Results in persistent or significant disability/incapacity (a substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect or
- Constitutes an important medical event that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed above.

4.9.1.4 Treatment-Emergent Adverse Events

Treatment-emergent AEs (TEAEs) will be defined as AEs that occur post first study drug dose or AEs noted prior to the first study drug administration that worsen after Baseline. Adverse events will be considered treatment emergent if the onset date is on or after the date of first dose study drug and on or prior to the date of last dose study drug + 28 days.

If the onset date of an AE is incomplete, then the event will be considered treatment-emergent if the month and year (or year alone if month is not recorded) of the event is:

- The same as or after the month and year (or year) of the first dose of study drug

If the start date of an AE is unknown, then the following rules will apply:

- If the AE onset is unknown and the end date is after the first dose of study drug or ongoing, then the AE will be considered treatment-emergent.
- If the AE onset date is unknown and the end date is before the first dose of study drug, then the AE will not be considered treatment-emergent.

- If both the start and end dates are unknown (or end date is ongoing), then the AE will be considered treatment-emergent.

For data presentation, SOC will be ordered alphabetically, with PT sorted by decreasing total frequency. The Safety Population will be used for all AE summaries. No inferential statistics will be provided for the AE data.

By-patient listings will be provided for AEs, SAEs, and AEs leading to study drug discontinuation.

4.9.2 Clinical Laboratory Assessments

The list of clinical laboratory assessments is included in Appendix D.
The number and percentage of subjects meeting at least 1 threshold analysis criterion event, during the TE period will be summarized by treatment group and overall. The threshold analysis criteria are provided in Appendix E.

All clinical laboratory data will be presented in listings.

Pregnancy test results for women of childbearing potential will be presented in listings only. Results from serology screen Hepatitis B surface antigen (HBsAG) and Hepatitis C virus antibody (HCV-Ab) will also be listed.

4.9.3 Vital Signs

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE will be summarized by treatment group and overall. The threshold analysis criteria are provided in Appendix E.

All vital signs data will be presented in a listing.

4.9.4 12-Lead ECG

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE period will be summarized by treatment group and overall. The threshold analysis criteria are provided in Appendix E.

A listing of all ECG results, including normality assessment (including clinical significance), abnormality details and ECG measurements, will be generated.

4.10 Protocol Violations or Deviations

Any protocol deviations and violations will be identified by the study team and archived in the TMF.

4.11 Missing Values – Missing Visits

Missing values will not be imputed unless otherwise specified.

4.12 Deviations from SAP

Any deviations from the original statistical plan will be described and justified in the final clinical study report.

4.13 Changes in Conduct or Planned Analyses from the Protocol

Due to the limited number of subjects being enrolled in the study, all model based analyses and summary statistics are no longer applicable and are therefore removed. For the same reason, lab, vital and ECG shift tables and summary statistics will not be created.

5 Tables and Listings

5.1 Table Format

All output will be produced using SAS version 9.2 or a later version.

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put below a horizontal line under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number,* programmers User ID, status of the table/listing (i.e. draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

A *landscape layout* is proposed for both table and listing presentations.

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9 cm from the right. The *top and bottom margins* will be a minimum 2.92 cm. *Header and footer* will be both 1.27 cm.

There is no special requirement of *font type* and *size*, but an *8-point* font size for tables and *7*or *8-point* for listings is proposed using *Courier New* font. A maximum SAS line size=141 and page size=44 for *8-point* font size, and line size=161 and page size=50 for *7-point* will be used so as to fit on both UK and US paper sizes.

In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number) must be presented at the beginning of that page.

5.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.

Data analyses will be presented as follows:

- For all serial assessments performed for adverse events, vital signs, ECG, efficacy endpoint, treatment exposure and compliance, and prior and concomitant medications data will be summarized by treatment.
- Disposition data will be summarized by treatment and overall.
- Demographics and baseline characteristics will be summarized by treatment and overall.
- Laboratory data will be summarized by treatment and overall.

Patient listings of all data from the eCRFs as well as any derived variables will be presented. In all patient listings, the relative day (i.e., relative to date of first dose of study drug) of all the dates will be presented.

Data collected at unscheduled visits will be included in the patient listings but will not be included in by-visit summary tables, unless otherwise specified. Data from unscheduled time points will be included in data summaries where indicated.

6 List of Tables, Figures and Listings

Table 14.1.1	Patient Disposition (All Randomized Patients)
Table 14.1.2	Demographic and Baseline Characteristics (Safety Population)
Table 14.1.3	Medical History (Safety Population)
Table 14.1.4.1	Treatment Exposure: 3 doses of CTP-656 or Placebo (Safety Population)
Table 14.1.4.2	Treatment Compliance: 3 doses of CTP-656 or Placebo (Safety Population)
Table 14.1.5.1	Summary of Prior Medications (Safety Population)
Table 14.1.5.2	Summary of Concomitant Medications (Safety Population)
Table 14.3.1.1	Overall Summary of Adverse Events (Safety Population)
Table 14.3.1.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.3	Treatment-related Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.4	Treatment Emergent Adverse Events by Maximum Severity (Safety Population)
Table 14.3.1.5	Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.6	Treatment Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.7	Treatment Emergent Adverse Events of Grade 3 or Higher Severity by System Organ Class and Preferred Term (Safety Population)
Table 14.3.2.1	Threshold Analysis of LFT during the TE period (Safety Population)
Table 14.3.2.2	Threshold Analysis of non LFT Biochemistry during the TE Period (Safety Population)
Table 14.3.2.3	Threshold Analysis of Haematology during the TE Period (Safety Population)
Table 14.3.3	Threshold Analysis of Vital Sign during the TE Period (Safety Population)
Table 14.3.4	Threshold Analysis of ECG during the TE Period (Safety Population)
Figure 14.2.1.1	Swimmer's Plot of Absolute Change from Baseline in Percent Predicted FEV1
Figure 14.2.2.1	Swimmer's Plot of Absolute Change from Baseline in Sweat Chloride
Figure 14.2.3.1	Swimmer's Plot of Absolute Change from Baseline in Cystic Fibrosis Questionnaire-Revised Respiratory Scale
Listing 16.2.1.1	Screen Failure (All Screened Patients)
Listing 16.2.1.2	Eligibility Criteria and Confirmation (All Screened Patients)
Listing 16.2.1.3	Patient Disposition (All Randomized Patients)
Listing 16.2.2.1	Demographics (All Randomized Patients)
Listing 16.2.2.2	Medical History (All Randomized Patients)
Listing 16.2.2.3.1	Accountability of Study Medications (All Randomized Patients)
Listing 16.2.2.3.2	Kalydeco Administration (All Randomized Patients)

Listing 16.2.2.4	Prior and Concomitant Medication (All Randomized Patients)
Listing 16.2.3.1	Sweat Chloride (All Randomized Patients)
Listing 16.2.3.2	Spirometry Measurements (All Randomized Patients)
Listing 16.2.3.3.1	Cystic Fibrosis Questionnaire-Revised Recorded Data (All Randomized Patients)
Listing 16.2.3.3.2	Cystic Fibrosis Questionnaire-Revised Domain Scale Scores (All Randomized Patients)
Listing 16.2.4.1	Adverse Events (All Randomized Patients)
Listing 16.2.4.2	Serious Adverse Events (All Randomized Patients)
Listing 16.2.4.3	Adverse Events Leading to Study Drug Discontinuation (All Randomized Patients)
Listing 16.2.4.4	Pulmonary Exacerbation Checklist (All Randomized Patients)
Listing 16.2.5.1	Laboratory Assessments: Hematology (All Randomized Patients)
Listing 16.2.5.2	Laboratory Assessments: Chemistry (All Randomized Patients)
Listing 16.2.5.3	Laboratory Assessments: Coagulation (All Randomized Patients)
Listing 16.2.5.4	Laboratory Assessments: Urinalysis (All Randomized Patients)
Listing 16.2.5.5	Serology Screen (All Randomized Patients)
Listing 16.2.5.6	Pregnancy Test (All Randomized Patients)
Listing 16.2.6	Vital Signs (All Randomized Patients)
Listing 16.2.7	12-Lead Electrocardiogram (All Randomized Patients)
Listing 16.2.8	12-Lead Electrocardiogram - Subjects with at Least 1 Abnormal (PCS) Findings (All Randomized Patients)

7 References

1. Vermeulen F, Camus CL, Davies JC, Bilton D, Milenkovic D, De Boeck K. Variability in sweat chloride concentration in subjects with cystic fibrosis and G551D mutations. J Cyst Fibrosis 2016; in press.
2. Mayer-Hamblatt N, Boyle D, VanDevanter D. Advancing clinical development pathways for new CFTR modulators in cystic fibrosis. Thorax 2016.
3. LeGrys VA. Assesing quality assurance for sweat chloride testing. J Am Soc for Med Tech1992;5:354-57.
4. United States Package Insert for Kalydeco, March 2015.

9 Appendices

Appendix A. Cytochrome P450 Drug Interactions

CYP P450 3A4/3A5/3A7 Inhibitors:	CYP P450 3A4/3A5 Inducers:
• Amiodarone • Aprepitant • Chloramphenicol • Cimetidine • Ciprofloxacin • Clarithromycin • Clotrimazole • Delaviridine • Diethyl-dithiocarbamate • Diltiazem • Erythromycin • Fluconazole • Fluvoxamine • Gestodene • Grapefruit juice • Imatinib • Indinavir • Itraconazole • Ketoconozole • Mifepristone • Nefazodone • Nelfinavir • Norfloxacin • Norfluoxetine • Ritonavir • Saquinavir • Star fruit • Telithromycin • Verapamil • Voriconazole	• Barbiturates • Carbamazepine • Efavirenz • Glucocorticoids • Modafinil • Nevirapine • Oxcarbazepine • Phenobarbital • Phenytoin • Pioglitazone • Rifabutin • Rifampin • St. John’s Wort • Troglitazone

Appendix D. Laboratory Assessments

<table>
<tr><th>HEMATOLOGY</th><th>CLINICAL CHEMISTRY</th><th>URINALYSIS</th></tr>
<tr><td rowspan="2">Complete blood count (CBC)
Platelet count
White blood cell (WBC) count with differential</td><td rowspan="2">Alanine aminotransferase (ALT)
Albumin (ALB)
Alkaline phosphatase (ALK-P)
Amylase
Aspartate aminotransferase (AST)
Total bilirubin
Direct bilirubin
Indirect bilirubin
Blood urea nitrogen (BUN)
Calcium (Ca)
Carbon Dioxide (CO_2)
Chloride (Cl)
Total cholesterol
Creatinine
Creatine kinase (CK)
Gamma-glutamyl transferase (GGT)
Glucose
Lactic dehydrogenase (LDH)
Lipase
Total serum protein
Phosphorus
Potassium (K)
Sodium (Na)
Uric Acid</td><td>Bilirubin
Glucose
Ketones
Nitrates
Occult Blood
Protein
Specific gravity
Urobilinogen
pH
Leukocytes
Microscopic urine analysis if dipstick positive</td></tr>
<tr><td>LFTs
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
Albumin
Gamma-glutamyl transferase
Total serum protein</td></tr>
<tr><th>SEROLOGY SCREEN</th><th>COAGULATION</th><th>PREGNANCY</th></tr>
<tr><td>Hepatitis B surface antigen (HBsAg)
Hepatitis C virus antibody (HCV-Ab)</td><td>Prothrombin Time Test (PT)
Partial Prothrombin Time Test (aPTT)
International normalized ratio (INR)</td><td>Human chorionic gonadotropin (hCG)</td></tr>
</table>

Appendix E. Threshold Analysis Criteria

Table 11-8 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.
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 - ≤ 2.5xULN >2.5 – ≤ 5.0xULN >5.0 – ≤ 20.0xULN >20.0xULN	CTCAE grade 1-4
Clinical Chemistry (NON-LFT)		

Table 11-8 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
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
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
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

Table 11-9 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
HR	Bradycardia	Per HV grade 2, 3, plus shift change
	<50 bpm	
	<45 bpm	
	Decrease from baseline ≥10 bpm	
	Decrease from baseline ≥20 bpm	
	<50 bpm and decrease from baseline ≥10 bpm	
	<50 bpm and decrease from baseline ≥20 bpm	
	Tachycardia	Per HV grade 1, 2, 3, plus shift change
	>100 bpm	
	>115 bpm	
	>130 bpm	
	Increase from baseline ≥10 bpm	
	Increase from baseline ≥20 bpm	
	>100 bpm and increase from baseline ≥10 bpm	
	>100 bpm and increase from baseline ≥20 bpm	
PR	≥240 ms	
	≥300 ms	
	≥200 ms and increase from baseline ≥40 ms	
	≥200 ms and increase from baseline ≥100 ms	
QRS	>110 ms	
	>160 ms	
	Increase from baseline ≥20 ms	
	Increase from baseline ≥40 ms	
QTc		To be applied to any kind of QT correction formula.
Borderline	>450 ms (Male) and <500ms; >470 ms and <500ms (Female)	
Prolonged*	≥500 ms	
Additional	Increase from baseline	
	Increase from baseline >10 ms	
	Increase from baseline >20 ms	
	Increase from baseline >40 ms	
	Increase from baseline >60 ms	

Note: Based on CPMP 1997 guideline.

Table 11-10 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
HR	Same as above in ECG category	
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	

Table 11-10 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	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	