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

INVESTIGATIONAL PRODUCT (IP):	CTP-656
PROTOCOL NUMBER:	CP656.2001
DATE FINAL:	July 15, 2016
AMENDMENT #1 DATE:	October 24, 2016
[redacted]	
SPONSOR NAME / ADDRESS:	Concert Pharmaceuticals, Inc. 99 Hayden Avenue, Suite 500 Lexington, MA 02421

CONCERT SIGNATURE PAGE

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

Protocol Number: CP656.2001

[redacted]

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

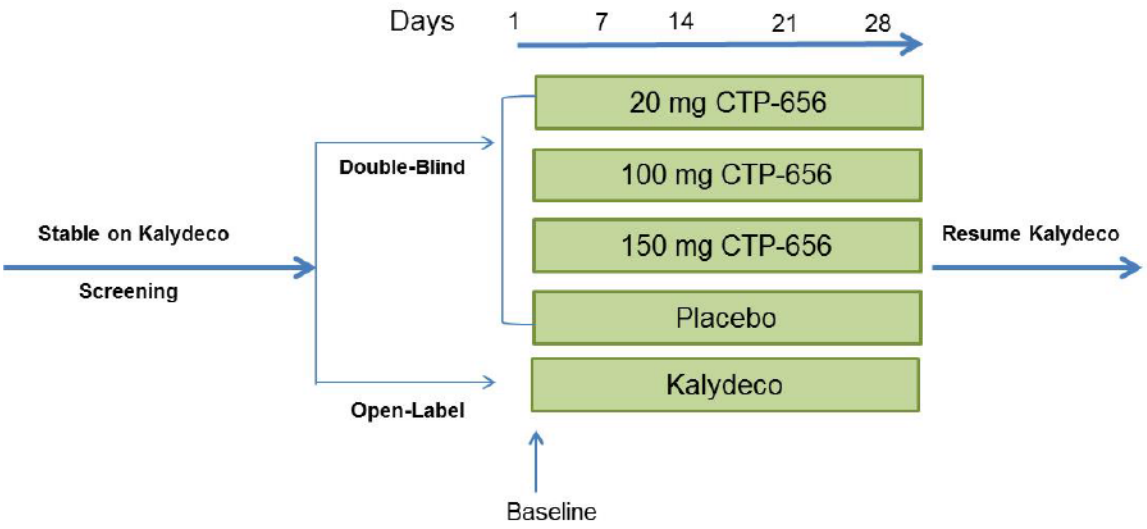
Protocol Number: CP656.2001

Signature of Principal Investigator	**dd mmm yyyy**
Printed Name of Principal Investigator **Institution Name:** By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Human Research Ethics Committees (IRBs or ECs) procedures, instructions from Concert representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

SYNOPSIS

Name of Sponsor/Company: Concert Pharmaceuticals	
Name of Investigational Product: CTP-656	
Name of Active Ingredients: CTP-656	
Title of Study: 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	
Study center(s): Multicenter study; approximately 15-20 sites	
Studied period (years): The estimated duration of the study is 15 months.	**Phase of development:** 2
Objective: 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.	
Methodology: This is a randomized, parallel-group, double-blind, placebo controlled multicenter study to evaluate the safety and efficacy of CTP-656 in patients with CF with CFTR gating mutations. The study will include an open-label active comparator, i.e., Kalydeco. Patients will be ≥ 18 years old, have been stable on Kalydeco therapy for at least 3 months prior to screening, and have a percent predicted forced expiratory volume in 1 second (FEV_1) ≥ 60% predicted for age, sex, and height, at screening and baseline (Day 1 of study treatment). There will be an opportunity for including patients with a percent predicted FEV_1 ≥ 50% predicted for age, sex, and height, at screening, if interim data reviewed by an independent Data Monitoring Committee (DMC) supports this. 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	

Methodology (continued):



Patients will return to the clinic on Day 1 (start of study treatment) for baseline assessments, including spirometry, sweat chloride, physical examination, and laboratory assessments including a baseline blood sample collection for pharmacokinetic (PK) evaluation (excluding open-label Kalydeco group).

Patients who continue to have percent predicted $FEV_1 \geq 60\%$ at the baseline (Day 1) assessment will be randomized to one of the five treatment groups.

Patients randomized to the double-blind CTP-656 or Placebo groups will be administered their dose in the clinic on Day 1 after consuming a small meal. Patients randomized to the open-label Kalydeco group will be instructed to take their dose in the clinic on Day 1 with fat-containing food as prescribed. All patients will remain in the clinic for safety/tolerability assessments. All patients (excluding open-label Kalydeco group) will be available for 2 separate blood collections for PK assessments; the first will be anytime between 30 minutes and 2 hours post-dose and the second collection will be anytime between 4 and 6 hours post-dose. The actual time collected will be recorded in each case. Patients will be instructed to continue to take their assigned study treatment each day after consuming a small meal for those on CTP-656 or Placebo, or fat-containing food for those on Kalydeco, for a total of 28 days. On Day 3, each patient will receive a phone call to discuss any adverse events (AEs) or other medical changes that may have occurred since Day 1.

Patients will return to the clinic on Day 7, Day 14, and Day 28 to complete assessments outlined in the Schedule of Events (Table 5.

Twenty-four hours after the administration of the last dose of CTP-656 or Placebo, all patients will resume taking Kalydeco as prescribed by the Investigator. Patients in the open-label Kalydeco group will continue taking Kalydeco as prescribed after the end of study treatment period (Day 28) One week after the last dose of study treatment (Day 35), patients will have a follow-up visit.

The safety of the subjects will be monitored throughout the study by the investigator and as spontaneously reported by the subject, in addition to the independent DMC. An interim analysis will be performed which will be described in the DMC Charter and the Statistical Analysis Plan (SAP). At any time during the study, patients who experience $\geq$ 10 percentage point decrease in percent predicted FEV_1 and/or have signs and symptoms

of pulmonary exacerbations as defined by the Fuchs criteria[1] may resume Kalydeco at the instruction and discretion of the Investigator. These patients will have Visit 5 safety, spirometry and CFQ-R assessments performed prior to resuming Kalydeco, if possible, and will be followed until the end of the study, as applicable.

Number of Subjects (planned):

Approximately 30-40 patients are planned to be enrolled, with approximately 6-8 patients randomized to each treatment group.

Main Criteria for Inclusion and Exclusion:

Patients eligible for enrollment in the study must meet all of the following inclusion criteria and none of the exclusion criteria:

Inclusion Criteria:

1. Is capable of giving written informed consent, ensuring that the patient will be compliant with the requirements and restrictions listed in the consent form and the protocol
2. Has a confirmed diagnosis of CF[2, 3], as determined by prior genotyping, with at least one allele of the following CFTR gating mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, and S549R. The CF mutations must be appropriately documented in the medical record
3. Has been stable on Kalydeco therapy for at least 3 months prior to screening
4. Is willing to remain off Kalydeco for 28 days if not assigned to the open label Kalydeco treatment arm
5. Is willing to remain on stable CF background therapy regimen as directed by physician/investigator for the duration of study participation
6. Has $FEV_1 \geq 60\%$ of predicted normal for age, sex, and height[4] at screening and baseline (Day 1) assessments
7. Is 18 years of age or older
8. Weighs at least 40 kg at screening
9. Patients of either gender and women of childbearing potential must be willing to use a medically highly effective form of birth control during the treatment period and 30 days after the last dose of study treatment. Examples of medically highly effective forms of birth control are:
    - Surgically sterile (via hysterectomy or bilateral ligation)
    - Has a male sexual partner who is sterile
    - Use of implants of levonorgestrel
    - Use of oral contraceptive (combined or progesterone only)
    - Use of double-barrier method (any combination of physical and chemical methods)
    - Use of any intrauterine device or other method with published data showing that the lowest expected failure rate is less than 1% per year (not all intrauterine devices meet this criterion)
10. If needed, has access to a care provider to provide assistance in completing study activities

Note: (a) Patients who do not meet the percent predicted $FEV_1 \geq 60\%$ criterion at the screening assessment may return for a reassessment of FEV_1 within 5 days. Patients who do not meet the $FEV_1 \geq 60\%$ criterion at the baseline assessment will not be eligible for enrollment.

Exclusion Criteria:

1. Acute upper respiratory infection within 14 days of the first dose of study treatment
2. Lower respiratory infection, pulmonary exacerbation, or changes in therapy (excluding inhaled antibiotics) for pulmonary disease within 4 weeks before the first dose of study treatment
3. Uncontrolled type 2 diabetes, or uncontrolled CF-related diabetes
4. History of hepatitis C or chronic active hepatitis B infection
5. History of pulmonary tuberculosis, non-tuberculosis mycobacterial infections or allergic bronchopulmonary aspergillosis (ABPA) treated during screening or within 2 years prior to screening
6. Colonization with *B. cenocepacia, B. dolosa, B. multivorans,* and/or *M. abcessus* within 2 years prior to Screening
7. Abnormal liver function at Screening, defined as ≥ 3 × upper limit of normal (ULN), of any 3 or more of the following: serum alanine transaminase (ALT), serum aspartate transaminase (AST), gamma-glutamyl transpeptidase (GGT), serum alkaline phosphatase (ALP), total bilirubin at screening
8. Are current smokers, or previous smokers with cessation less than 6 months before screening
9. History of abnormal renal function (creatinine clearance < 50 mL/min using the Cockgroft-Gault equation)
10. History of prolonged QT/QTc interval with Fridericia's correction (QTcF) > 450 msec for males or QTcF > 470 msec for females at screening
11. History of solid organ or hematological transplantation
12. History of alcohol, medication, or illicit drug abuse within 1 year before screening
13. Currently participating in another therapeutic clinical study or previously participated in an investigational drug study within 30 days before screening
14. Using any inhibitor or inducer of cytochrome P450 3A during the study or within 30 days of screening
15. Women who are pregnant or lactating, or have plans to become pregnant during the study or within 1 month following the last dose
16. Unable or unwilling to comply with study requirements
17. History of any illness or condition that, in the opinion of the investigator might confound the results of the study or pose an additional risk in administering CTP-656 to the patient

Investigational Product, Dosage and Mode of Administration:

CTP-656: 20 mg, 100 mg or 150 mg, taken orally, once daily, with a small meal.

Reference Therapy, Dosage and Mode of Administration:

Kalydeco: 150 mg, taken orally, once every 12 hours with fat-containing food

Placebo: Taken orally, once daily, with a small meal.

Duration of Study Participation:

Patients will be screened within 14 days of administration of first dose of study treatment (Day 1) and if eligible will be randomized to 1 of the 5 treatment groups. Patients will be

treated double-blind with 1 of 3 doses of CTP-656, or Placebo, or will remain on open-label Kalydeco for 28 days; 1 week after the last dose of study treatment, patients will have a follow-up visit. Therefore, each patient's study participation (including the screening period) will be up to approximately 49 days or 7 weeks in duration.

Criteria for Evaluation:

Efficacy will be primarily assessed by changes in sweat chloride. Changes in percent predicted FEV_1, and quality of life using the Cystic Fibrosis Questionnaire-Revised (CFQ-R) will also be assessed. Safety and tolerability will be evaluated by monitoring AEs, and by results of physical examinations, vital signs, electrocardiograms, and clinical laboratory tests.

Efficacy Measures

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]

Where:

baseline is the measurement prior and closest to the administration of the first of treatment on Day 1, and change = value at scheduled day – value at baseline

Safety Measures

Safety and tolerability of study treatment will be evaluated by monitoring AEs, and by results of physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory tests. Adverse events will be coded by Medical Dictionary for Regulatory Activities system organ class and preferred term. Concomitant medications will be coded by World Health Organization Drug Dictionary Anatomical-Therapeutic-Chemical classification and preferred drug name.

Statistical Methods:

Analysis Populations:

The Safety Population is defined as all randomized patients who receive at least one dose of

study treatment. Efficacy analyses will be based on the Full Analysis Population, which is defined as all patients in the Safety Population with at least 1 post-baseline measurement of sweat chloride.

Sample Size

Estimates for the standard deviation of change from baseline in sweat chloride were obtained from 4 sources[5,6,7,8]. 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.

Analysis of Efficacy Measures

Efficacy endpoints will be summarized by treatment group and timepoint, and will be analyzed by timepoint using analysis of covariance (ANCOVA) with a fixed effect for treatment and with the corresponding baseline value as a covariate, with a test of the treatment effect at a two-sided significance level of 0.05, as follows:

1. Each of CTP-656 dose groups (20 mg, CTP-656 100 mg, CTP-656 150 mg) vs. Placebo
2. CTP-656 20 mg vs. CTP-656 150 mg, CTP-656 20 mg vs. 100 mg, CTP-656 100 mg vs. CTP-656 150 mg
3. Each of CTP-656 dose groups (20 mg, CTP-656 100 mg, CTP-656 150 mg) vs. Kalydeco
4. Kalydeco vs. Placebo

All statistical tests will be 2 tailed with Type I error = 0.05. Given that this is a Phase 2, exploratory dose-ranging study, no adjustment for multiple comparisons will be made.

Handling of missing values and additional details on the methods of analyses will be specified in the Statistical Analyses Plan (SAP).

Analysis of Safety Measures

Safety endpoints will be summarized descriptively. No formal statistical tests will be performed.

Adverse events (AEs), vital sign measurements, physical examination findings, clinical laboratory information and concomitant medications will be tabulated and summarized by treatment group. Separate summaries will be produced for all treatment-emergent AEs, treatment-related AEs (those considered by the Investigator as related (definitely, probably, possibly), see Section 13.2), serious AEs (SAEs), discontinuations due to AEs, and AEs ≥ Grade 3 severity, according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. By-patient listings will be provided for any deaths, SAEs, and AEs leading to discontinuation of treatment.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or special term	Explanation
ABPA	allergic bronchopulmonary aspergillosis
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}24hr}$	area under the plasma concentration-time curve from time 0 to 24 hours post-dose
$AUC_{0\text{-}inf}$	area under the plasma concentration-time curve from time 0 to infinity
C_{24hr}	concentration 24 hours following a single dose
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFR	Code of Federal Regulations
CFTR	cystic fibrosis transmembrane conductance regulator
C_{max}	maximum plasma concentration
CRF/eCRF	case report form/electronic case report form
CRO	clinical research organization
CTCAE	Common Terminology Criteria for Adverse Events
CTP-656	D9-ivacaftor
CYP	cytochrome P450
DMC	Data Monitoring Committee
DMP	data management plan
EC	Ethics Committee
ECG	Electrocardiogram
EDC	electronic data capture
EENT	eyes/ears/nose/throat
FAS	Full Analysis Set

Abbreviation or special term	Explanation
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
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Probability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IP	investigational medicinal product
IRB	Institutional Review Board
IXRS	Interactive Response System
MedDRA	Medical Dictionary for Regulatory Activities
PHI	protected health information
PK	pharmacokinetic(s)
QoL	quality of life
QTcF	Fridericia-corrected QT interval
SAE	serious adverse event
SDV	source document verification
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	apparent terminal half-life
T_{max}	Time to reach maximum plasma concentration
ULN	upper limit of normal
WHO	World Health Organization

2. INTRODUCTION

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. The CFTR protein is an epithelial chloride channel responsible for aiding in the regulation of salt and water absorption and secretion in various tissues. Gating mutations result in a CFTR protein with a primary defect of low channel open probability compared to normal CFTR. The G551D mutation is the most common gating mutation worldwide, and when paired with another mutation associated with minimal CFTR function (e.g. F508del), will most often result in a severe CF clinical phenotype.

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.

Kalydeco was first approved by the U.S. Food and Drug Administration (FDA) in January 2012 for use in people with CF ages 6 and older who have at least one copy of the G551D mutation. Kalydeco was subsequently approved by the European Medicines Agency (EMA) in July 2012, Health Canada in November 2012, and by the Australian Therapeutic Goods Administration (TGA) in July 2013 for the same indication. In February 2014, Kalydeco was approved by the FDA for use in people with CF ages 6 and older who have the following additional CFTR mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P and G1349D. In December 2014, Kalydeco was approved for use in patients suffering from CF aged six years and above with an R117H mutation. In March 2015, Kalydeco was approved by the U.S. FDA for use in CF patients aged two to less than six years who have one of the following mutations in the CFTR gene: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D and R117H.

CTP-656 is a deuterated isotopolog of ivacaftor that has demonstrated an improved PKprofile in non-clinical studies as well as Phase 1 studies in healthy volunteers, enabling once daily dosing in the clinical setting.

The CTP-656 Investigator's Brochure (IB) can be consulted for more detailed technical information, discussion of nonclinical evaluations, and relevant information regarding the known and theoretical safety profile.

[redacted]

3. 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.

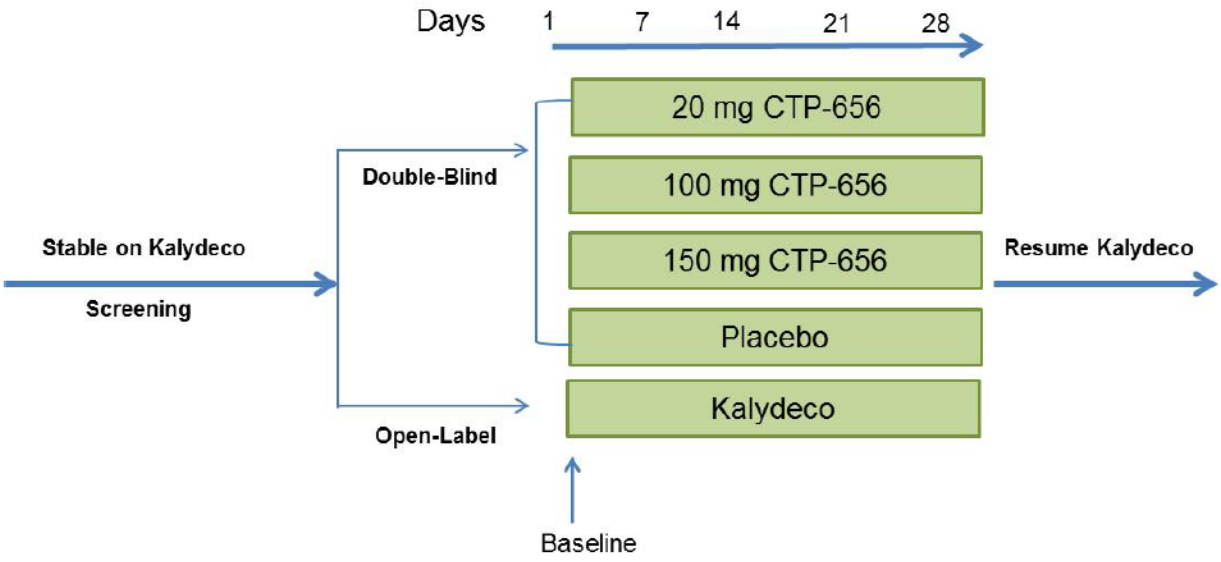
4. OVERALL STUDY DESIGN

4.1. 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 ≥ 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 4: Study Design



Patients will return to the clinic on Day 1 (start of study treatment) for a review of eligibility criteria and for baseline assessments, including spirometry, sweat chloride, physical examination, and laboratory assessments including a baseline blood sample collection for PK evaluation (excluding open-label Kalydeco group).

Patients who have percent predicted $FEV_1 \geq 60\%$ at the baseline (Day 1) assessment will be randomized to one of the five treatment groups. Patients who do not meet the percent predicted $FEV_1 \geq 60\%$ criterion at the baseline assessment will not be enrolled.

Patients who are randomized to the double-blind CTP-656 or Placebo groups will be dispensed appropriate study treatment and will take the first dose in the clinic on Day 1 after consuming a small meal. Patients who are randomized to the open-label Kalydeco group will take their dose of Kalydeco in the clinic on Day 1 after consuming fat-containing food as prescribed. Each patient will remain in the clinic for safety and tolerability assessments. Patients (excluding open-label Kalydeco group) will be available for blood collection for PK assessments at 1 time point each within of the following 2 time windows post-dose (1) between 30 minutes and 2 hours post-dose and (2) between 4 and 6 hours post-dose. Patients will be instructed to continue taking CTP-656 or Placebo each day (once a day) after a small meal for a total of 28 days. Patients in the open-label Kalydeco group will be instructed to continue taking Kalydeco after consuming fat-containing food as prescribed for 28 days.

On Day 3, each patient will receive a phone call to discuss any adverse events (AEs) or other medical changes that may have occurred since Day 1.

Patients will return to the clinic on Day 7, Day 14, and Day 28 to complete assessments outlined in the Schedule of Events (Table 5). On Day 21 patients will receive a phone-call to discuss any adverse events (AEs) or other medical changes that may have occurred between study visit days.

Twenty-four hours after the last dose of CTP-656 or Placebo, patients will resume taking Kalydeco as prescribed by the Investigator. Patients in the open-label Kalydeco group will continue taking Kalydeco as prescribed after the end of study treatment period (Day 28). One week after the administration of the last dose of study treatment (Day 35), each patient will have a follow-up visit.

The safety of the subjects will be monitored throughout the study by the DMC. An interim analysis will be performed which will be described in the DMC Charter and the Statistical Analysis Plan (SAP).

Patients who experience ≥ 10 percentage point decrease in percent predicted FEV_1 and/or signs and symptoms of pulmonary exacerbations as defined by the Fuchs criteria[1] at anytime during the study may resume Kalydeco at the instruction and discretion of the Investigator. These patients will have Visit 5 safety, spirometry and CFQ-R assessments performed prior to resuming Kalydeco, if possible, and will be followed until the end of the study, as applicable.

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.

Efficacy will be assessed by changes in sweat chloride and percent predicted FEV_1, and quality of life will be assessed using the CFQ-R. Safety and tolerability will be evaluated by monitoring AEs, and by results of physical examinations, vital signs, electrocardiograms, and clinical laboratory tests. Blood/plasma concentrations of CTP-656 and its metabolites may also be assessed.

[redacted]

4.3. Study Duration

Patients will be screened within 14 days of administration of first dose of study treatment (Day 1) and if eligible will be randomized (1:1:1:1:1) to one of the 5 treatment groups: (1) Double-blind CTP-656 20 mg for 28 days (2) Double-blind CTP-656 100 mg for 28 days (3) Double-blind CTP-656 150 mg for 28 days (4) Double-blind Placebo for 28 days (5) Open-label Kalydeco for 28 days. One week after the last dose of study treatment, each patient will have a follow-up visit. Therefore, each patient's study participation (including the screening period) will be up to approximately 49 days or 7 weeks in duration.

4.4. End of Trial

The End of Trial is defined as the date of the last visit of the last patient required for primary and/or secondary analysis, as specified in the protocol and/or the Statistical Analysis Plan.

5. STUDY PROCEDURES

5.1. Schedule of Events

The schedule of events is provided in Table 5.

Table 5: 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
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 2, 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

[redacted]

5.2. Study Procedures

5.2.1. Visit 1, Day -14 to Day -1 (Screening Visit)

Patients will undergo a screening examination between Day -14 and Day -1.

Prior to performing any study-related activities or evaluations, the patient must be thoroughly informed about all aspects of the study, including scheduled visits and activities. Patients will sign the study-specific consent form(s) prior to any screening procedure. Patients will be instructed to report all AEs that occur during the study from the time of informed consent forward.

Patients should continue to perform airway clearance procedures and take their stable CF therapy regimen per their regular schedule during the screening period.

The following information and procedures will be performed and documented as part of the screening assessment:

- Informed consent and, where applicable, Health Insurance Probability and Accountability Act (HIPAA) authorization
- Assessment of eligibility according to inclusion/exclusion criteria. The CF mutation genotype should be appropriately documented in the medical record.
- Demographics, including sex, ethnic origin, and date of birth, if permitted, according to local regulations.
- Medical history, including query for baseline signs/symptoms (ie, an AE with onset prior to dosing is to be recorded as a pretreatment AE)
- Review of concomitant medications (taken 30 days prior to screening) including stable CF background therapy regimen
  - Patients who are on prescribed inhaled cycling antibiotics should start Day 1 of the 28-day cycle on Day 1 of CTP-656 or Placebo treatment
- Complete physical examination plus height and weight
- Vital signs measured including blood pressure, pulse rate, respiratory rate, and temperature
- Standard 12-lead ECG
- Blood samples for clinical chemistry, hematology, coagulation, and hepatitis B and C evaluations
- Serum Pregnancy tests for women of childbearing potential
- Urinalysis (see Appendix A)
- Spirometry assessment (preferably pre-bronchodilator, see Section 9.1)
  - Patients who do not meet the percent predicted $FEV_1 \geq 60\%$ criterion may return for a reassessment of percent predicted FEV_1 within 5 days

Compliance with inclusion criteria (listed in Section 6.2) and exclusion criteria (listed in Section 6.3) will be verified against information collected and documented in the source documents and the electronic case report form (eCRF). Local laboratory results obtained at screening will be used to verify eligibility.

5.2.2. Treatment Period

Patients should continue to perform airway clearance procedures prior to visits and take their stable CF background therapy regimen per their regular schedule during the treatment period with the exception of Kalydeco if randomized to a CTP-656 or Placebo treatment group.

Patients who are on prescribed inhaled cycling antibiotics should start Day 1 of the 28-day cycle on Day 1 of study treatment if randomized to a CTP-656 or Placebo treatment group. Patients who are randomized to the open-label Kalydeco group should continue their inhaled cycling antibiotic treatment regimen as scheduled.

5.2.2.1. Visit 2, Day 1 (Start of treatment)

The following baseline assessments will be performed and documented:

- Cystic Fibrosis Questionnaire-Revised (CFQ-R; should be the first assessment at visit)
- Spirometry assessment prior to dose of CTP-656, Placebo or Kalydeco (preferably pre-bronchodilator, see Section 9.1)
  - Patients are required to meet the $FEV_1 \geq 60\%$ criterion prior to randomization
  - Patients who do not meet the percent predicted $FEV_1 \geq 60\%$ criterion will not be enrolled
- Following confirmation of eligibility, consenting patients will be randomized to 1 of the 5 study treatment groups
- Update of medical history including query for baseline signs/symptoms. Reports of AEs that occur before or on Day 1 prior to dosing will be noted as "pretreatment" on the eCRF; otherwise, all reported AEs will be post-treatment
- Review of concomitant medications including stable CF background therapy regimen
- Abbreviated physical examination, including weight
- Vital signs measured including blood pressure, pulse rate, respiratory rate, and temperature
- Standard 12-lead ECG
- Blood samples for safety laboratory testing (hematology, clinical chemistry, and coagulation)
- Urine pregnancy test for women of childbearing potential
- Sweat chloride assessment prior to dose of CTP-656, Placebo or Kalydeco

- Dispensation of CTP-656 or Placebo tablets
- Patients should bring their Kaldyeco supply to the clinic
- Administration of first dose of CTP-656 or Placebo in the clinic after consumption of a small meal
- Patients who are randomized to the open-label Kalydeco group will take their dose in the clinic after consumption of fat-containing food
- Blood sample for PK assessments (excluding open-label Kalydeco group); predose, and at 2 post-dose time points
  - Time window 1: anytime between 30 minutes and 2 hours post-dose, and
  - Time window 2: anytime between 4 and 6 hours post-dose
  - Note: Actual collection times will be recorded
- Patients randomized to CTP-656 or placebo should be instructed to take their dose each day after consuming a small meal while patients remaining on Kalydeco should be instructed to take their dose each day with fat-containing food as prescribed. Instructions to bring all used and unused CTP-656, Placebo tablets to all study visits; reminder for the open label Kalydeco arm subjects to bring Kalydeco tablets to study visits
- Instructions that dose of CTP-656, Placebo or Kalydeco should be taken in the clinic on visit days
- Reminder that the patient will receive a phone call on Day 3 to discuss any AEs or other medical changes that may have occurred since Day 1
- Instructions to return to clinic for Visit 3 (Day 7)

5.2.2.2. Telephone Call, Day 3

On Day 3, each patient will receive a phone call to discuss any possible AEs or other medical changes that may have occurred since the Day 1 visit.

5.2.2.3. Visit 3, Day 7 and Visit 4, Day 14

The following assessments will be performed and documented:

- Monitoring of AEs (ie, query of any AEs that have occurred since prior visit and follow up on ongoing AEs)
- Review of concomitant medications including stable CF therapy regimen
- Abbreviated physical examination depending on patient symptoms, including weight
- Vital signs measured including blood pressure, pulse rate, respiratory rate, and temperature
- Standard 12-lead ECG

- Blood samples for safety laboratory testing of LFTs (ALT, AST, total and direct bilirubin, alkaline phosphatase, albumin, total serum protein and GGT; Visit 4 only)
- Administration of dose of CTP-656 or Placebo in the clinic (Visit 3 and 4) after consumption of a small meal
- Patients who are randomized to the open-label Kalydeco group will take their dose in clinic after consumption of fat-containing food
- Sweat chloride assessment within 4 hours post CTP-656, Placebo or Kalydeco dose
- Spirometry assessment within 4 hours post CTP-656, Placebo or Kalydeco dose (preferably pre-bronchodilator, see Section 9.1)
- Blood sample for PK assessments (Visit 4 only; excluding open-label Kalydeco group): predose, and at 2 post-dose time points
  - Time window 1: anytime between 30 minutes and 2 hours post-dose, and
  - Time window 2: anytime between 4 and 6 hours post-dose
  - Note: Actual collection times will be recorded
- Patients randomized to CTP-656 or placebo should be instructed to take their dose each day after consuming a small meal while patients on Kalydeco should be instructed to take their dose each day with fat-containing food as prescribed. Assessment of CTP-656 or Placebo compliance via tablet count
- Instructions to bring all used and unused CTP-656 or Placebo tablets to all study visits; reminder for the open label Kalydeco arm subjects to bring Kalydeco tablets to study visits
- Instructions to return to the clinic for Visits 4 (Day 14) and 5 (Day 28)

5.2.2.4. Telephone Call, Day 21

On Day 21, each patient will receive a phone call to discuss any possible AEs or other medical changes that may have occurred since the Day 14 visit.

5.2.2.5. Visit 5, Day 28 (End of Treatment Visit), or Early Termination

The following assessments will be performed and documented at the final treatment visit; patients who prematurely discontinue the study will be encouraged to complete the Visit 5 safety, spirometry and CFQ-R assessments prior to stopping study treatment, if not contraindicated:

- CFQ-R (should be the first clinical assessment at visit)
- Monitoring of AEs (ie, query of any AEs that have occurred since prior visit and follow up on ongoing AEs)
- Review of concomitant medications including stable CF background therapy regimen

- Abbreviated physical examination depending on patient symptoms, including weight (full physical examination including height and weight for Early Termination)
- Vital signs measured including blood pressure, pulse rate, respiratory rate, and temperature
- Standard 12-lead ECG
- Blood samples for safety laboratory testing (hematology, clinical chemistry, and coagulation).
- Urinalysis
- Urine pregnancy test for women of childbearing potential (serum pregnanacy test for Early Termination)
- Administration of dose of CTP-656 or Placebo in the clinic after consumption of a small meal (not for Early Termination)
- Patients who are randomized to the open-label Kalydeco group will take their dose in clinic after consumption of fat-containing food (not for Early Termination)
- Sweat chloride assessment within 4 hours post CTP-656, Placebo or Kalydeco dose (not for Early Termination)
- Spirometry assessment within 4 hours post CTP-656, Placebo or Kalydeco dose (preferably pre-bronchodilator, see Section 9.1)
- Blood sample for PK assessments (excluding open-label Kalydeco group; not for Early Termination): predose, and at 2 post-dose time points
  - Time window 1: anytime between 30 minutes and 2 hours post-dose, and
  - Time window 2: anytime between 4 and 6 hours post-dose
  - Note: Actual collection times will be recorded
- Assessment of CTP-656 or Placebo compliance via tablet count
- Collection of all used and unused CTP-656 or Placebo tablets

Following completion of all Visit 5 procedures, patients will have completed the treatment period. As prescribed by the Investigator, patients on the CTP-656 or Placebo groups will resume Kalydeco 24 hours after the administration of the last dose of CTP-656 or Placebo. Patients in the open-label Kalydeco group will continue taking Kalydeco per their prescription.

5.2.2.6. Visit 6, Day 35 (Follow-Up)

One week after the administration of the last dose of study treatment the patients will have a follow-up visit. The following asssessments will be performed and documented.

- Monitoring of AEs (ie, query of any AEs that have occurred since prior visit and follow up on ongoing AEs)

- Review of concomitant medications including resumption of Kalydeco and any other new medications since prior visit
- Full physical examination including height and weight
- Vital signs measured including blood pressure, pulse rate, respiratory rate, and temperature
- Standard 12-lead ECG
- Blood samples for safety laboratory testing (hematology, clinical chemistry, and coagulation).
- Serum pregnancy test for women of child bearing potential

All attempts will be made that patients with unresolved AEs at the time of Visit 6 will be contacted regularly until AE is resolved (see Section 13).

6. STUDY POPULATION

6.1. Number of Patients and Sites

This is a multicenter study; approximately 15-20 study sites are planned.

Approximately 30-40 patients with CF who have a CFTR gating mutation (G1244E, G1349D,G178R, G551S, S1251N, S1255P, S549N, or S549R), are ≥ 18 years old, have been stable for 3 months on Kalydeco therapy prior to the screening, and have $FEV_1 \geq 60\%$ predicted for age, sex and height at screening will be enrolled in this study. There will be an opportunity for including patients with a percent predicted $FEV_1 \geq 50\%$ predicted for age, sex, and height, at screening, if interim data reviewed by the Data Monitoring Committee (DMC) supports this.

6.2. Inclusion Criteria

Patients must satisfy the following criteria to be enrolled in the study:

1. Is capable of giving written informed consent ensuring that patient will be compliant with the requirements and restrictions listed in the consent form and the protocol
2. Has a confirmed diagnosis of CF[2,3], as determined by prior genotyping, with at least one allele of the following CFTR gating mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, and S549R. The CF mutations must be appropriately documented in the medical record
3. Has been stable on Kalydeco for at least 3 months
4. Is willing to remain off Kalydeco for 28 days if randomized to the CTP-656 or Placebo groups
5. Is willing to remain on stable CF background therapy regimen for the duration of study participation
6. Has $FEV_1 \geq 60\%$ of the predicted for age, sex, and height (Hankinson) at screening and baseline (Day 1) assessments
7. Is 18 years of age or older
8. Weighs at least 40 kg at screening
9. Patients of either gender and women of childbearing potential must be willing to use a medically highly effective form of birth control during the treatment period and 30 days after the last dose of study treatment.
   Examples of medically highly effective forms of birth control are as follows:
   - Surgically sterile (via hysterectomy or bilateral ligation)
   - Has a male sexual partner who is surgically sterilized
   - Use of implants of levonorgestrel
   - Use of oral contraceptive (combined or progesterone only)
   - Use of double-barrier method (any combination of physical and chemical methods)
   - Use of any intrauterine device or other method with published data showing that the lowest expected failure rate is less than 1% per year (not all intrauterine devices meet this this criterion)

10. If needed, has access to a caretaker to provide assistance in completing study activities. Note: (a) Patients who do not meet the $FEV_1 \geq 60\%$ criterion at the screening assessment may return for a reassessment within 5 days. Patients who do not meet the $FEV_1 \geq 60\%$ criterion at the baseline assessment will not be eligible for enrollment.

6.3. Exclusion Criteria

The presence of any of the following will exclude a patient from enrollment:

1. Acute upper respiratory infection within 14 days of the first dose of study treatment
2. Lower respiratory infection, pulmonary exacerbation, or changes in therapy (excluding inhaled antibiotics) for pulmonary disease within 4 weeks before first dose of study treatment
3. Uncontrolled type 2 diabetes, or uncontrolled CF-related diabetes
4. History of hepatitis C or chronic active hepatitis B infection
5. History of pulmonary tuberculosis, non-tuberculosis mycobacterial infections or allergic bronchopulmonary aspergillosis (ABPA), treated during screening or within 2 years prior to screening
6. Colonization with *B. cenocepacia, B. dolosa, B. multivorans, and/or M. abcessus* within the last 2 years prior to Screening
7. Abnormal liver function at Screening, defined as $\geq 3 \times$ upper limit of normal (ULN), of any 3 or more of the following: serum alanine transaminase (ALT), serum aspartate transaminase (AST), gamma-glutamyl transpeptidase (GGT), serum alkaline phosphatase (ALP), total bilirubin
8. Are current smokers, or previous smokers with cessation less than 6 months before screening
9. History of abnormal renal function (creatinine clearance < 50 mL/min using the Cockgroft-Gault equation)
10. History of prolonged QT/QTc interval with Fridericia's correction (QTcF) > 450 msec for males or QTcF>470 msec for females at screening
11. History of solid organ or hematological transplantation
12. History of alcohol, medication, or illicit drug abuse within 1 year before screening
13. Currently participating in another therapeutic clinical study or previously participated in an investigational drug study within 30 days before randomization
14. Using any inhibitor or inducer of cytochrome P450 3A during the study or within 30 days of screening
15. Women who are pregnant or lactating, or have plans to become pregnant during the study or within 1 month following the last dose
16. Unable or unwilling to comply with study requirements

17. History of any illness or condition that, in the opinion of the investigator might confound the results of the study or pose an additional risk in administering CTP-656 to the patient

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Study Treatments

CTP-656 will be formulated as a white, film-coated oval tablet containing 20, 75, or 100 mg of CTP-656. CTP-656 will be processed to a stabilized amorphous state which is then incorporated into the tableting process. Each CTP-656 tablet will contain the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropylmethylcellulose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, PEG 3350, polyvinyl alcohol, sodium lauryl sulfate, talc, and titanium dioxide. The matching placebo for CTP-656 tablets will contain the same inactive ingredients as the CTP-656 tablet, with the exception of hydroxypropylmethylcellulose acetate succinate.

The active comparator product, Kalydeco tablet, 150 mg, will be the marketed dosage form.

7.2. Study Treatment Administration and Schedule

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 6: 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

7.3. Method of Study Treatment Assignment

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

Once a randomization number has been assigned to a patient, it will not be reassigned to any other patient.

7.4. Packaging and Labeling

CTP-656 tablets (20 mg, 75 mg, 100 mg), and Placebo tablets, will be packaged in PVC/Aclar blister packs. All products should be stored at room temperature in the original packaging. A stability study will run concurrent with the clinical study to support continued use of the clinical trial material.

The labels for the study treatments will include sponsor name, address, and telephone number, the protocol number, study treatment name, dosage form and strength (where applicable), amount of study treatment per container, lot number, expiration/retest date as applicable, medication identification /kit number, storage conditions, and required caution statements and/or regulatory statements, as applicable. Additional information may be included on the label, as applicable, per local regulations.

7.5. Investigational Product Accountability and Disposal

All study treatments should be stored in a secure, locked area, under the responsibility of the Investigator or other authorized individual until dispensed to the patients.

Study treatment must be stored in the original package at room temperature as stated on the package label. No special handling procedures are required.

The Investigator or designee must maintain accurate records of the receipt of all study treatment, including date received, lot number, expiration/retest date as applicable, amount received, condition of the package, and the disposition of all study treatment.

Current dispensing records will also be maintained, including the date and amount of medication dispensed to each individual patient. Returned study treatment records will be maintained and final study treatment reconciliation will also be recorded for each patient.

Concert (or designee) will review with the Investigator and relevant site personnel the process for study treatment return, disposal, and/or destruction, including responsibilities for the site versus Concert (or designee).

7.6. Study Treatment Compliance

Compliance will be monitored for study treatment accountability (CTP-656 and Placebo) throughout the study firstly by the investigative site and secondly by Concert or its designee. All patients should strive for 100% compliance with the dosing schedule and documentated retraining should occur in cases of non-compliance. The Medical Monitor should be consulted if compliance drops below 80% at any visit. All study treatment not used in the study must be destroyed by the study site or returned to Concert or its designee after the study is completed.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

All medications, including over-the-counter therapies (eg, vitamins, herbal and nutritional supplements), taken in the 30 days prior to screening will be recorded in the patient's source documentation and documented in the eCRF.

The medications permitted during the study will be those that the patients have been taking as part of their stable CF background therapy regimen 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 B). These compounds must not have been taken within 30 days of Day 1 and may not be administered as a concomitant medication. Use of oral, injectable, or implant contraceptives is permitted for female patients.

9. EFFICACY PROCEDURES

9.1. Pulmonary Function

Spirometry will be performed according to American Thoracic Society guidelines[10]. During the study, including the Screening Period, FEV_1 measurements should be performed pre-bronchodilator administration, and on Day 1 (baseline assessment), prior to administration of study treatment. Thereafter spirometry assessments should be performed within 4 hours after administration of study treatment and preferably at the same time of day at each visit including the baseline (Day 1) visit.

Pre-bronchodilator spirometry is defined as spirometry testing performed for a patient who has:

- Witheld their short-acting β-agonist (e.g., albuterol) or anticholinergic (e.g., Atrovent®) for more than 4 hours before the spirometry assessment; AND
- Witheld their long-acting bronchodilator (e.g., salmeterol) for more than 12 hours before the spirometry assessment; AND
- Witheld their once-daily, long-acting bronchodilator (e.g., tiotropium bromide [Spiriva®]) for more than 24 hours before the spirometry assessment

The time and date of all pre-spirometry doses of bronchodilators taken within the previous 24 hours will be recorded for each spirometry assessment.

In the event that a patient forgets to withhold bronchodilators, spirometry should be performed according to the following:

- During the Screening Period, if a patient forgets to withhold their dose of bronchodilator, spirometry should be performed post-bronchodilator and all subsequent spirometric measurements (Days 1, 7, 14 and 28) should be performed pre-bronchodilator
- If a patients's Day 1 spirometry is pre-bronchodilator, but on a subsequent the patient forgets to withhold the bronchodilator, a post-bronchodilator spirometry will be obtained for that visit only and the visit will not be rescheduled
- If on Day 1 the patient forgets to withhold their dose of bronchodilator, spirometry should be performed post-bronchodilator and all subsequent spirometric measurements (Days 7, 14 and 28) should be performed post-bronchodilator
- Each spirometry assessment will be recorded in the source documents as pre-bronchodilator or post-bronchodilator

The following parameters will be recorded as part of the spirometry assessment (according to Hankinson standards):

- FEV_1: liter and percent predicted for age, gender and height
- Forced vital capacity (FVC): liter and percent predicted for age, gender and height

- Forced expiratory flow over the middle half of the FVC (FEF_{25-75}): liter/second and percent predicted for age, gender, and height

9.2. Sweat Chloride Analysis

The sweat test, the major diagnostic tool of cystic fibrosis, measures sweat electrolyte levels, including chloride, using quantitative pilocarpine iontophoresis. The sweat chloride concentration of an untreated patient with cystic fibrosis is typically ≥ 60 mmol/L. Intermediate concentrations of 40-59 mmol/L may be observed in patients with CF but are considered diagnostically indeterminate. Sweat chloride concentrations ≤ 39 mmol/L are generally considered normal, although CF patients have been observed with these low concentrations, particularly at very young ages.

To ensure consistency and reproducibility in this multicenter study, sweat secretions will be collected at each site according to the standardized procedure of the Macroduct® Model 3700 Collection System (Wescor, Inc. Logan, Utah), with standardized solutions provided to each site. Two sweat collections, 1 from each arm, will be obtained from each patient at each time point. Sweat samples will be analyzed and interpreted at a central laboratory. Specific instructions for collection, handling, and processing of sweat chloride samples to the central analysis and reading center will be provided in a separate manual.

The sweat chloride test will be conducted within 4 hours of CTP-656, Placebo or Kalydeco dose except at the Day 1 visit when the sweat chloride test should be performed prior to administration of CTP-656, Placebo or Kalydeco dose. Analyses will be performed using the chloride value obtained from the collection with the greater amount of sweat at each time point. If only one of the collections is available, this value will be used.

9.3. Health-Related Quality of Life

Patients will complete the adult version of the CFQ-R, a validated disease-specific instrument that measures health-related quality of life (QoL) for persons with CF[11], in their native language. [redacted] Validated translations of the CFQ-R will be provided for participating sites in non-English-speaking countries, if applicable The CFQ-R consists of 50 items across 12 domains, i.e., 9 QoL dimensions (physical functioning, role, vitality, emotional functioning, social, body image, eating disturbances, treatment burden, and health perceptions) and 3 symptom scales (weight, respiratory symptoms, and digestive symptoms). Responses are provided on a 4-point Likert scale and rescaled within each domain to a score range from zero to 100 points, with higher scores representing better health. For the CFQ-R, a minimal clinically important difference of at least 4 points has been established for the respiratory domain[12]. The CFQ-R will be administered on Day 1 (Baseline) and Day 28 (End of study treatment administration or Early Termination) and must be completed prior to the start of any assessments scheduled at the visit and prior to the dose of CTP-656, Placebo or Kalydeco on each of those days.

10. SAFETY PROCEDURES

10.1. Physical Examination

A complete physical examination, including assessment of the following body systems: head/neck/thyroid, eyes/ears/nose/throat (EENT), chest, lungs, heart, lymph nodes, abdomen, skin, musculoskeletal, and neurological systems will be performed by qualified personnel at the screening visit, Visit 2 (Day 1) and Visit 5 (Day 28 or early termination). A symptom-directed examination will be performed on Visit 3 (Day 7), Visit 4 (Day 14), and Visit 5 (Day 28). Weight (kilograms) will be measured as part of all physical examinations. Height (centimeters) will be measured only at the screening visit.

10.2. Vital Signs

Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature, will be measured at each study visit, after the patient has rested for approximately 5 minutes.

10.3. Electrocardiograms

Twelve-lead ECGs will be performed (see Section 12.9.5) at screening and each treatment visit. All scheduled ECGs will be performed after the patient has rested for approximately 5 minutes.

ECGs must be evaluated for safety by the Investigator or his/her designee. If clinically significant abnormalities are recorded, ECGs will be repeated at the discretion of the Investigator.

10.4. Clinical Laboratory Assessments

The list of clinical laboratory assessments is included in Appendix A.

Virus serology (hepatitis B surface antigen, and hepatitis C virus antibodies) will be assessed at the screening visit.

Clinical laboratory tests (clinical chemistry, hematology, coagulation, and urinalysis) will be performed according to the schedule of assessments and analyzed at the site's local laboratory. The results of clinical laboratory tests conducted during screening must be assessed by the Investigator to determine each patient's eligibility for participation in the study. The Investigator should indicate review of the laboratory reports by signing and dating the report. Any significant abnormalities should be fully investigated. Whenever possible, the etiology of the abnormal findings will be documented on the eCRF. Laboratory results with significantly abnormal values should be repeated for verification. Additional tests or other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an AE should be obtained when clinically indicated. In particular, if a clinically significant abnormal result is observed that is not resolved by the final study visit, repeat tests will be performed if possible and resolution or stability of the abnormality will be recorded in the source documentation.

Any significant laboratory abnormalities that are either serious or unexpected will be promptly reported to Concert Pharmaceuticals' representative. Any additional relevant laboratory results

obtained by the Investigator during the course of this study will be reported to Concert Pharmaceuticals or its representative.

11. PHARMACOKINETIC ASSESSMENTS

11.1. PK Blood Sample Collection

Blood samples for PK analysis will be collected from all study groups except the open-label Kalydeco group at 3 times per visit on Day 1, Day 14 and Day 28 (Visits 2, 4 and 5). The time of last dose of CTP-656 or Placebo prior to the blood collection and the exact time of the blood collection must be recorded for each sample. The PK schedule requires 1 predose, and 2 post-dose draws, each within a distinct post-dose window. The following schedule for PK draws should be observed:

- Predose (a blood collection before in-clinic dosing for all patients enrolled in the study
- Window 1: between 30 minutes and 2 hours post-dose (1 draw at any time within the specified window)
- Window 2: between 4 and 6 hours post-dose (1 draw at any time within the specified window)

A total of 9 PK samples should be taken for a patient in the CTP-656 or Placebo group that completes the study. All attempts to adhere to the PK schedule should be made. However, the inability to follow the schedule or to obtain/process a sample will not be considered a protocol deviation.

Details for PK blood sample processing will be detailed in a separate laboratory manual.

11.2. Plasma Sample Storage and Shipping

Details will be provided in a separate laboratory manual.

11.3. Bioanalytical Methodology for Determination of Plasma Concentrations

Plasma concentrations of CTP-656 and its metabolites, D-M1 and D-M6 will be measured using validated bioanalytical methods using LC/MS/MS techniques and according to the bioanalytical laboratory's standard operating procedures (SOP).

12. STATISTICAL ANALYSES

12.1. Overview

A statistical analysis plan will be written that will detail all analyses that will be performed for this study, including the tables, figures, and data listings to be generated. The statistical analysis plan will be finalized prior to the interim analysis.

12.2. Interim Analysis

An interim analysis will be performed which will be described in the DMC Charter and the SAP.

12.3. Determination of Sample Size

Estimates for the standard deviation of change from baseline in sweat chloride were obtained from 4 sources[5,6,7,8]. 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.

12.4. Analysis Populations

The Safety Population will include all randomized patients who receive at least one dose of study treatment. This population will be used for baseline characteristics and for safety data summaries. Efficacy analyses will be based on the Full Analysis Population Set (FAS), which include all patients in the Safety Population with at least 1 post-baseline measurement of sweat chloride.

Unscheduled collections/measurements may not be included in the summaries, but will be presented in the patient listings.

12.5. Background and Demographic Characteristics

Demographics and medical history will be collected during screening and summarized, including the date the patient signed the initial informed consent. The patients' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) and summarized using frequency tabulations by system organ class and preferred term. 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 (see Section 6.2).

12.6. Patient Disposition

Patient disposition (analysis population allocation, randomized, discontinued, along with primary reason for discontinuation, completed) will be summarized using frequency and percentage. Protocol deviations will be summarized using frequency tabulations.

12.7. Efficacy Analysis

The efficiacy endpoints that will be measured are:

Primary Endpoint

- Change from baseline in sweat chloride at Day 28

Secondary Endpoints

- Change from baseline in percent predicted FEV_1 at Day28
- Change from baseline in CFQ-R Respiratory Domain at Day 28

[redacted]

Where:

baseline is the measurement prior and closest to the administration of the first of treatment on Day 1, and change = value at scheduled day – value at baseline

Efficacy endpoints will be summarized by treatment group and timepoint, and will be analyzed by timepoint using analysis of covariance (ANCOVA) with a fixed effect for treatment and with the corresponding baseline value as a covariate, with a test of the treatment effect at a two-sided significance level of 0.05, as follows:

1. Each of CTP-656 20 mg, CTP-656 100 mg, CTP-656 150 mg vs. Placebo
2. CTP-656 20 mg vs. CTP-656 150 mg, CTP-656 20 mg vs. 100 mg, CTP-656 100 mg vs. CTP-656 150 mg
3. Each of CTP-656 20 mg, CTP-656 100 mg, CTP-656 150 mg vs. Kalydeco
4. Kalydeco vs. Placebo

All statistical tests will be 2 tailed with Type I error = 0.05. Given that this is a Phase 2, dose-ranging study, no adjustment for multiple comparisons will be performed.

Handling of missing values and additional details on the methods of analyses will be specified in the SAP.

[redacted]

12.8. Pharmacokinetic Analysis

PK analyses may be performed as appropriate.

12.9. Safety Analysis

Safety evaluations will be based on the incidence, intensity, and type of AEs including clinically significant changes in the patient's physical examination findings, vital signs, ECGs, and clinical laboratory results. Safety variables will be tabulated and presented for all patients in the Safety Population. Data will be summarized by treatment group. Exposure to study treatment, dosing compliance, and reasons for discontinuation of study treatment will be tabulated.

12.9.1. Adverse Events

Adverse events will be summarized by MedDRA system organ class and preferred term by treatment group.

Separate summaries will be produced for all treatment-emergent AEs (AEs that occur post first study drug doseor AEs noted prior to the first study drug administration that wosen after Baseline), treatment-related AEs (those considered by the Investigator as suspected; see Section 13.2), SAEs, discontinuations due to AEs, and AEs ≥ Grade 3 severity, according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. By-patient listings will be provided for any deaths, SAEs, and AEs leading to discontinuation of treatment.

12.9.2. Concomitant Medications

Concomitant medications will be summarized by World Health Organization (WHO) Drug Dictionary Anatomical-Therapeutic-Chemical (ATC) classification and preferred drug name by treatment group.

12.9.3. Physical Examination

All abnormal physical examination findings will be documented in the eCRF. Results of physical examinations will be listed by patient.

12.9.4. Vital Signs

Vital signs will be summarized at each time point for each treatment group, using descriptive statistics. Change from baseline in vital signs values will also be summarized. Mean (SD) temporal profiles for vital signs (systolic and diastolic blood pressure and pulse rate) may be presented graphically.

12.9.5. Electrocardiogram

From the 12-lead ECG data, heart rate, PR, QRS, QT, and Fridericia-corrected QT interval (QTcF) will be reported for each time point and summarized using descriptive statistics. Mean (SD) temporal profiles for 12-lead ECG (QT and QTcF) may be presented graphically. The frequency (number) of clinically significant findings may be reported and summarized by treatment group.

12.9.6. Clinical Laboratory Assessments

Subjects with clinically significant abnormal laboratory values will be identified. Clinically significant laboratory values (i.e., meets ≥ Grade 3, according to CTCAE, version 4.0) will be summarized by treatment group. Laboratory values will also be evaluated for any potential trends within/across treatments groups.

12.9.7. Study Treatment Compliance

Dosing compliance (CTP-656 and placebo) will be assessed by comparing the number of doses scheduled and those taken by each patient. If a patient only takes a partial dose at an occasion, he/she will not be counted as taking all of his/her study treatment. Descriptive statistics will be used to summarize the dosing compliance percentage within each treatment group.

The number of patients exposed to each study treatment will be summarized using descriptive statistics.

13. ADVERSE EVENTS

13.1. Monitoring, Recording, and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a patient during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the patient's health, including laboratory test values, regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and AE should be reported as separate terms.

All patients will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the patient's clinical symptoms including pulmonary exacerbations (as defined by Fuch's criteria), cutaneous reactions/rash, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

An adverse event reported after consent but before the day of the first dose of study treatment, ie, Day 1, is to be documented by the Investigator as a pretreatment AE. An adverse event recorded on the first day of dosing but before any study treatment dose is taken will also be recorded as a pretreatment AE. Adverse events will be considered treatment emergent if the onset date and time is after the first dose of study treatment.

All AEs will be recorded by the Investigator until end of study or resolution of AE. AEs and SAEs will be recorded on the AE page of the eCRF and in the patient's source documents. All SAEs must be reported to Concert's designated Drug Safety Unit and Medical Monitor within 24 hours of the Investigator's knowledge of the event by facsimile or other appropriate method using the SAE Report Form or approved equivalent form.

13.2. Evaluation of Adverse Events

A qualified Investigator at the site will evaluate all AEs as to seriousness, severity/intensity, causality, duration, action taken, and outcome. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0[13] will be used for grading the severity of Adverse Events. A copy of the CTCAE will be provided in the Safety Manual.

13.2.1. Seriousness

An SAE is any AE occurring at any dose that fulfills the following criteria, as per Title 21 Code of Federal Regulations (CFR) 312.32 and International Conference on Harmonisation (ICH) E2A.II.B.

- 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.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the patient or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to study treatment, action taken regarding study treatment, and outcome.

13.2.2. Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/intensity of the event.

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on patient/event *outcome* or *action* criteria associated with events that pose a threat to a patient's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

13.2.3. Causality

The Investigator must determine the relationship between the administration of study treatment and the occurrence of an AE/SAE as reasonable possibility of relatedness and no reasonable possibility of relatedness, as defined below:

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The event, including an abnormal laboratory test result, occurs in a plausible time relationship to study drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The event resolves or improves upon withdrawal of study drug (de-challenge). The event would be considered as definitely related to the study drug upon results of a positive re-challenge procedure.

Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other concomitant treatments, and follows a clinically reasonable response on withdrawal (dechallenge), if dechallenge was done.

Possibly Related: There is evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the event (e.g., the patient's clinical condition, other concurrent disease, concomitant medications or events).

Unlikely Related: An event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (eg, the event did not occur within a reasonable time after administration of the study drug) and in which other drugs or concurrent or underlying disease provide plausible explanations (eg, the patient's clinical condition, other concomitant treatments).

Not related: The event is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

13.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

13.2.5. Action Taken

The Investigator will record the action taken with the study treatment as a result of an AE or SAE on the case report form, as applicable (eg, discontinuation, interruption, or reduction of CTP-656 dose, as appropriate) and record if concomitant and/or additional treatments were given for the event.

13.2.6. Outcome

All AEs that have not resolved upon discontinuation of the patient's participation in the study must be followed in accordance with the Principal Investigator's and Medical Monitor's judgment until resolution, but non-related AEs will be followed in accordance with the Principal Investigator's and Medical Monitor's judgment.

13.2.7. Assessment of Expectedness

Each SAE that is Suspected to be related to the study treatment must be assessed for expectedness by the Sponsor to determine whether it is reportable as a SUSAR (Suspected Unexpected Serious Adverse Reaction). The Reference Safety Information (RSI) for this study, against which expectedness assessments are made, can be found in the IB. Determination of the expectedness of an event is the responsibility of the Sponsor.

13.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of study treatment, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as an SAE.

If a laboratory abnormality is 1 component of a diagnosis or syndrome, only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

13.4. Pregnancy

If a patient or male patient's partner becomes pregnant any time during the treatment period the appropriate form should be used to report the pregnancy to Investigator, Sponsor or its designee. Patient pregnancies (or pregnancy of a male patient's partner) must be followed until termination of pregnancy or for a minimum of 6 months following the birth of the child.

13.5. Adverse Event Documentation

13.5.1. Adverse Event Recording and Reporting

Each individual AE is to be listed as a separate entry on the AE eCRF. The Investigator will provide information about dates of onset and resolution, seriousness, severity, frequency, action(s) taken, outcome, and relationship to CTP-656.

Documentation of immediately reportable events will follow procedures described in Section 13.6.

The Investigator must report to Sponsor or its designee all AEs that occur during the study from the time written informed consent is given until the final study visit or early termination, regardless of their relationship to CTP-656.

If an Investigator becomes aware of an SAE within 30 days after the last dose of study treatment is administered, the event must be documented and reported, as described in Section 13.6.

13.5.2. Follow-up of Adverse Events and Serious Adverse Events

All AEs assessed as not related to CTP-656 or procedure, including clinically significant laboratory tests, ECGs, or physical examination findings, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the final study visit occurs, whichever comes first. Adverse events assessed as related to CTP-656 or procedure will be followed for as long as necessary to adequately evaluate the patient's safety, until the event stabilizes, or the patient is lost to follow up. If resolved, a resolution date should be provided. The Investigator is responsible for ensuring that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional clinical laboratory testing or investigations, examinations, or consultation with other health care professionals as is practical.

Any SAE brought to the attention of the Investigator within 30 days after cessation of CTP-656 or study procedure and considered by him/her to be caused by CTP-656 with a reasonable possibility, should be reported through the SAE reporting process.

13.6. Reporting of Serious Adverse Events

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are believed to be related to an Investigational Product (IP) and are both unexpected (ie, the nature or severity is not expected from the information provided in the IB) and serious. SUSARs are subject to expedited reporting to the Sponsor, Sponsor's designee, regulatory authorities, and the Institutional Review Board (IRB) or Ethics Committee (EC) (see Section 13.6.2 for reporting details on reporting SUSARs).

In addition to SUSARs, other safety issues may qualify for expedited reporting if they might materially alter the current benefit-risk assessment of study treament or would be sufficient to consider changes in the administration of the study treatment or in the overall conduct of the study, for instance:

- An increase in the rate of occurrence or a qualitative change of an expected SAE, which is judged by the Principal Investigator in consultation with the Sponsor and the Medical Monitor to be clinically important
- SAEs that occur after the patient has completed the clinical study and the Sponsor considers them to be a SUSAR
- New events related to the conduct of the study or the development of the study treatment and likely to affect the safety of the patients, such as:
  - an SAE that could be associated with the study procedures and that could modify the conduct of the study
  - a significant hazard to the patient population such as lack of efficacy of study treatment used for the treatment of a life-threatening disease
  - a major safety finding from a newly completed animal study (such as carcinogenicity)
  - any anticipated end or temporary halt of a study for safety reasons and conducted with the same study treatment in another country by the same Sponsor.

13.6.1. Urgent Safety Measures

If the study site staff becomes aware of an actual or potential urgent safety issue, then the Sponsor and Sponsor's designee (Medical Monitor) must be immediately contacted so that appropriate urgent safety measures can be agreed upon. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of patients participating in a clinical trial
- A serious risk to human health or potentially a serious risk to human health

An urgent safety issue may include: (i) issues with an investigational drug or comparators, (ii) study procedures, (iii) inter-current illness (including pandemic infections), (iv) concomitant medications, (v) concurrent medical conditions, or (vi) any other issues related to the safe conduct of the study or that pose a risk to study patients.

In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, the Investigators may take urgent safety measures before informing the Sponsor, but the Sponsor must be informed immediately after the hazard has resolved.

13.6.2. Reporting

- Reporting SAEs - The Investigator is responsible and required to report all SAEs within 24 hours after becoming aware of the occurrence of an SAE or serious adverse reaction. All SAE reporting will be done electronically via electronic data capture (EDC). This will be done on the AE eCRF by ticking the box, "Is the event Serious"

as "yes". The investigator will then be prompted to complete additional fields to capture the event. The EDC will electronically notify the study Sponsor and the Sponsor's designated Pharmacovigilance Department. Reporting of SUSARs - It is the responsibility of the Sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify the Investigator of its decision as soon as possible.

- Expedited Reporting of Events - It is the responsibility of the Sponsor to determine whether an event requires expedited reporting and to notify the Investigator of its decision as soon as possible. When expedited reporting is required, the following procedures should be followed.
  - Fatal or life-threatening SUSARs - It is the responsibility of Sponsor or its designee to report fatal or life-threatening SUSARs to regulatory authorities as soon as possible, but no later than 7 calendar days after Sponsor first becomes aware of the reaction. All SAE reporting will be done electronically via EDC. The Investigator is required to notify the IRB or EC of any SUSAR as soon as possible, but no later than 7 calendar days after first becoming aware of the reaction. Any additional relevant information should be updated in EDC system within 8 days after the date of submission of the initial the report.
  - Other SUSARs - It is the responsibility of Sponsor or its designee to report other SUSARs to regulatory authorities as soon as possible, but no later than 15 calendar days after the date the Sponsor first becomes aware of the reaction.
  - The Investigator is required to notify the IRB or EC of any other SUSAR as soon as possible, but no later than 15 calendar days after first becoming aware of the reaction.
- **Reporting of Urgent Safety Issues** - The Sponsor or its designee is required to inform the appropriate competent authorities, Investigators, and IRB or EC within 3 calendar days after it becomes aware of the urgent safety issue.
- **Serious Breaches** - It is the responsibility of the clinical site and staff to notify the Sponsor and Sponsor's designee immediately upon becoming aware of a serious breach of GCP or of the study protocol. It is the responsibility of the Sponsor or its designee to notify regulatory authorities of any serious breach which is likely to effect, to a significant degree, the safety or mental integrity of the patients of the study or the scientific value of the study. The Sponsor or its designee will notify the regulatory authorities within 7 days after becoming aware of a serious breach.

13.6.3. Safety Queries

Queries pertaining to SAEs will be communicated via the EDC system. The response time is expected to be no more than 5 business days. Urgent queries (eg, missing causality assessment must be answered at the time of reporting/entering the data into the EDC system.

13.7. Expedited Reporting of Adverse Events

13.7.1. Immediately Reportable Experiences

The following events may occur during participation in this clinical study and must be reported to the Sponsor immediately:

- Death or other SAE
- Pregnancy of a patient or patient's partner (during the treatment period)

The events listed above must be reported within 24 hours after first knowledge of the event by study personnel to the appropriate Sponsor contacts provided below, or other designated Sponsor designee. For immediately reportable experiences, the appropriate form (eg, SAE Report Form, Pregnancy Form, Drug Discrepancy Form) should be completed as thoroughly as possible and signed by the Investigator or his/her designee before transmittal to Sponsor or its designee. For SAEs, it is important that the Investigator provide his/her assessment of causality to study treatment or procedure at the time of the initial report. If the Investigator's assessment of causality changes then a follow-up SAE form must be submitted.

Contact Person (USA):
[redacted], MD [redacted]
[redacted]
[redacted] (office)
(mobile)
(after hours answering service)

14. DISCONTINUATIONS

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 5) and will be followed, as applicable.

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

Patients who are in the double-blind CTP-656 or Placebo groups may resume Kalydeco at the instruction and discretion of the Investigator if they experience ≥ 10 percentage point decrease in absolute percent predicted FEV_1 and/or have signs and symptoms of pulmonary exacerbations as defined by the Fuchs criteria[1]:

- Clinical need for new or change in antibiotics (oral, intravenous or inhaled) as indicated by presence of at least 4 or 12 possible signs or symptoms:
  - Change in sputum volume or color
  - New or increased haemoptysis
  - Increased cough
  - Increased dyspnea
  - Increased malaise, fatigue or lethargy
  - Temperature over 38°C
  - Anorexia or weight loss
  - Sinus pain or tenderness
  - Change in sinus discharge
  - Change in physical findings on examination of the chest
  - Decrease in pulmonary function by 10% or more
  - Radiographic changes

Patients who resume Kalydeco due to the reasons outlined above will have Visit 5 safety, spirometry and CFQ-R assessments prior to resuming Kalyedco, if possible, and will be followed until the end of the study, as applicable.

Patients in the open-label Kalydeco group who experience ≥ 10 percentage point decrease in absolute percent predicted FEV_1 and/or have signs and symptoms of pulmonary exacerbations[1] should be referred to their primary CF physcican.

It is strongly recommended that all patients with ALT or AST elevations of ≥ 3 × ULN and clinical-symptoms be followed closely, including repeat confirmatory testing within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT and AST level, as clinically indicated. Study treatment must be interrupted immediately and the Medical Monitor must be notified if any of the following criteria are met:

- ALT or AST > 5 × ULN
- ALT or AST > 3 × ULN for more than 2 weeks
- Total bilirubin > 2 × ULN and/or clinical jaundice, in association with elevation of ALT or AST > 3 × ULN

A thorough investigation of potential causes should be conducted and the subject should be followed closely for clinical progression. Patients discontinued for elevated transaminases should be followed until their transaminases normalize or return to baseline.

In addition, patients should be withdrawn if they:

- Experience a serious, intolerable or life-threatening AE
- Develop a clinically significant laboratory or ECG abnormality
- Require a medication that is prohibited by the protocol
- Do not follow guidelines specified in the protocol (ie, is noncompliant with protocol procedures or study treatment administration)
- Are lost to follow-up
- Do not continue to meet certain entry criteria or meets certain exclusion criteria during the course of the study

Adverse events resulting in termination will be followed to the satisfactory resolution and determination of outcome, as ascertained by the Investigator (and/or Sponsor, or its designee). The data will be recorded on the appropriate eCRF.

14.1. Handling of Early Terminations

If a patient terminates early from the study, either at his or her request or at the Investigator's discretion, the Investigator will record the reason(s) for early termination on the relevant eCRF page and notify the Sponsor immediately. The specific reason for the withdrawal should be carefully documented on the eCRF.

All attempts should be made to obtain follow-up data on any patient who is terminated because of an AE including pulmonary excaerbations, abnormal laboratory test, or ECG finding.. Sites should document attempts to follow patients including evidence of a registered letter in cases where patients are lost to follow-up.

14.2. Sponsor's Termination of Study

The Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

Such a termination must be implemented by the Investigator, if instructed to do so by the Sponsor, in a time frame that is compatible with the patient's well-being.

15. EMERGENCY PROCEDURES

15.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Concert Clinical Research personnel or designee by telephone at the number(s) listed in the Study Reference Manual.

15.2. Emergency Unblinding of Treatment Assignment

In the case of an adverse event for which it is medically required to break the blind in order to determine appropriate treatment, unblinding can be achieved by using the IXRS. A study subject for whom the blind is broken should stop the treatment of study drug prematurely. The Medical Monitor must be notified immediately of the blind break.

16. REGULATORY CONSIDERATIONS

16.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by GCP, as described in ICH Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from IRB or EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

16.2. Sponsor's Responsibility

The Sponsor or its designee is responsible for the following:

1. Selecting qualified Investigators
2. Providing Investigators with the information they need to properly conduct an investigation
3. Ensuring proper monitoring of the investigation
4. Ensuring that the applicable regulatory authorities, and all participating Investigators are properly informed of significant new information regarding AEs or risks associated with the medication being studied

As the Sponsor, Concert Pharmaceuticals has delegated some responsibilities to a designee, or contract research organization (CRO).

16.3. Audits and Inspections

The Sponsor's Quality Assurance Unit (or representative) may conduct audits at the study site(s). Audits will include, but are not limited to: drug supply, presence of required documents, the informed consent process, laboratory specimen processing, and comparison of CRFs/eCRFs with source documents. The Investigator agrees to cooperate with audits conducted at a reasonable time and in a reasonable manner.

Regulatory authorities worldwide may also audit the Investigator during or after the study. The Investigator should contact the Sponsor immediately if this occurs, and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

The Investigator is required to make all study documentation promptly available for inspection, review or audit at the study site upon request by Sponsor, its representatives, or any appropriate regulatory agencies.

16.4. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. The Sponsor staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, and study treatments, as well as study-related duties and functions. The Investigator should maintain a list of Sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all patients who sign an informed consent document and are screened for entry into the study. Patients who fail screening must have the reason(s) recorded in the patient's source documents.

The Investigator or a designated member of the Investigator's staff must be available during monitoring visits to review data, resolve queries, and allow direct access to patient records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

17. ETHICS

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor and the Investigator conduct the study in accordance with GCP, (as defined by ICH guidelines and directives, and applicable local regulatory requirements and laws, including Title 21 CFR Parts 50, 56, and 312). Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki, Tokyo 2013.

Copies of these materials are available from the Sponsor and the Sponsor's designee upon request. The purpose of these regulations, legal obligations, and guidances is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

1. Human patients are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not.
2. The study is conducted with diligence and in conformance with the protocol in such a way as to protect patient safety and ensure the integrity of the findings.
3. The potential benefits of the research justify the risks.

The Investigator is responsible for protecting the rights, safety, and welfare of patients under his/her care, and for the control of the medications under investigation.

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, CTP-656, and their study-related duties and functions. The Investigator will maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties. Individuals ineligible to conduct or work on clinical studies, including those ineligible as a result of debarment under the Generic Drug Enforcement Act of 1992, will not be allowed to conduct or work on studies sponsored by Concert Pharmaceuticals. The Investigator is required to immediately disclose to the Sponsor in writing if any person involved in the conduct of the study is debarred pursuant to a hearing by the United States Food and Drug Administration under this anti-fraud law, or if any proceeding for debarment is pending, or is (to the best of the Investigator's knowledge) threatened.

The rest of this section of the protocol describes in more detail the specific GCP-defined responsibilities the Investigator assumes by agreeing to participate in this study.

17.1. Ethics Review

The Investigator (or designee) must submit this study protocol, the Sponsor's approved Informed Consent Form (ICF), patient information sheets, patient recruitment materials, and other appropriate documents to IRB or EC, and following review of the submitted materials, is

required to forward to the Sponsor (or designee) a copy of the written and dated approval/favorable opinion signed by the appropriate IRB or EC designee.

The approval/favorable opinion should clearly state the trial (study number, protocol title, and version number), the documents reviewed (eg, protocol, ICF, IB) and the date of the review.

The study will not commence at the study site until the Sponsor has received a copy of this written and dated approval/favorable opinion.

During the trial, any amendment to the protocol and the ICF (as appropriate) should be submitted to IRB or EC. The IRB or EC should also be informed of any event likely to affect the safety of patients or the continued conduct of the trial, in particular any change in safety. Additionally, all updates to the IB will be sent to IRB or EC. A progress report will be sent to IRB or EC and the protocol will be reviewed annually (eg, re-approved) or more frequently, as required by IRB or EC or local regulations.

The Investigator will notify the IRB or EC of the conclusion of the clinical study within 1 month of completion or termination of the study. The final report sent to IRB or EC will also be sent to the Sponsor along with the completed eCRFs and all necessary regulatory documents, thereby fulfilling the Investigator's regulatory responsibility.

The Investigator will maintain a copy of all correspondence with the IRB or EC, including copies of approved documents. The Investigator will also maintain a copy of the IRB or EC membership list with occupation and qualification (or a statement confirming compliance with GCP requirements for committee composition). An IRB or EC General Assurance Number may be accepted in lieu of a membership roster.

Any advertisements used to recruit patients for the study must be approved by the Sponsor and IRB or EC prior to use.

17.2. Ethical Conduct of the Study

Before the first patient is enrolled in the study, all ethical, regulatory, and legal requirements must be met.

An Investigator participating in this study is required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable local regulations related to the conduct of a clinical study.

Participating Investigators, including members of the Committees and National Coordinators, will receive compensation for their time but will receive no financial profit from their activities related to the trial.

17.3. Patient Information and Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the patient or patient's legally authorized representative, as applicable, in accordance with local practice and regulations. Written informed consent must be obtained from all patients participating in a clinical study conducted by the Sponsor.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the patient must be explained to the patient. The patient must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the patient, must be given to the patient. Confirmation of a patient's informed consent must also be documented in the patient's source documentation prior to any testing under this protocol, including screening tests and assessments.

Each consent form should contain an authorization allowing the Principal Investigator(s) and the Sponsor to use and disclose protected health information (PHI) in compliance with local law.

The original signed consent form will be retained with the study records.

17.4. Confidentiality

All information disclosed or provided by the Sponsor (or designee) produced during the trial including, but not limited to, the protocol, the eCRFs, the IB, and the results obtained during the course of the trial (if applicable), are confidential. The Investigator or any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, submission of this protocol and any other necessary documentation to IRB or EC is expressly permitted, IRB or EC members having the same obligation of confidentiality.

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. However, authorized regulatory officials and sponsor personnel (or designee) will be allowed full access to inspect and copy the records. The copied and inspected records will remain at the site and will not be transmitted or removed from the site. All CTP-656, patient bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor and responsible ethics committee(s) or regulatory authorities.

Patients will be identified only by unique patient numbers in eCRFs. Their full names may, however, be made known to a regulatory agency or other authorized officials in the event of inspections. Documents containing the full name or other personally identifiable information of the patient are to remain at the site. This information will not be transferred to the Sponsor or be contained in regulatory filings. In the event of inspections by authorized agencies, this patient identification may be disclosed.

17.5. Patient Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (eg, PHI authorization in North America).

The patient will not be identified by name in the eCRF or in any study reports and these reports will be used for research purposes only. The Sponsor, its partner(s) and designee(s), and various government health agencies may inspect the records of this study. Every effort will be made to keep the patients' personal medical data confidential.

The Sponsor will protect individual patient information to the fullest extent possible during this trial. At no time will a patient become identified in any publication or presentation. However, the patient may have to become identified in the event of a Regulatory Authority audit or inspection in order to verify the accuracy of the data. Access to patient information is at the discretion of the Sponsor and cannot occur prior to database lock or other specified events, as determined solely by the discretion of the Sponsor.

17.6. Protocol Amendments

The Investigator will not make any changes to this protocol without prior written consent from the Sponsor and subsequent approval by IRB or EC. Any permanent change to the protocol, whether an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol that appears necessary as the study progresses will be fully discussed by the Investigator(s) and the Sponsor. If agreement is reached regarding the need for an amendment, it will be written by the Sponsor. The written amendment must be submitted to the chairman of IRB or EC identified with this responsibility. Except for administrative amendments, Investigators must await IRB or EC approval of protocol amendments before implementing the change(s). Administrative amendments are defined as having no effect on the safety of the research patients, scope of the investigation, or quality of the trial. However, a protocol change intended to eliminate an apparent immediate hazard to patients should be implemented immediately, and IRB or EC notified within 5 days. The Sponsor will ensure submission of any protocol amendments to the appropriate regulatory agencies.

When, in the judgment of the chairman of the local IRB or EC, the Investigators, and/or the Sponsor, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the patient, the currently approved written ICF will require similar modification. In such cases, repeat informed consent will be obtained from patients enrolled in the study before expecting continued participation.

17.7. Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or IRB or EC, the Investigator must submit to IRB or EC:

- Information on serious or unexpected AEs as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to patients.

17.8. Closure of the Study

The Sponsor reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB or EC, regulatory authorities).

In addition, the Sponsor has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

18. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by the Sponsor or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

A quality-control and quality-assurance plan addressing aspects of the trial that may impact data integrity or the protection of human patients may be instituted for this study. All audit findings will be summarized and placed on file with appropriate documentation of response/resolution.

19. DATA HANDLING AND RECORDKEEPING

19.1. Data Collection

Data obtained for analysis in the clinical study described in this protocol will be documented in the eCRF. All primary data generated by central laboratories will become part of the final study dataset. All non-eCRF datasets (eg, PK results) will be reconciled, as appropriate, against the eCRF, queried and cleaned, prior to Database Lock. Data reported in the eCRFs should be consistent with and substantiated by the patient's medical record and original source documents. Any discrepancies must be explained. Unless explicitly allowed in the eCRF instructions, blank data fields are not acceptable. If a field is blank because the item was not done, the field will be marked "Not Done." If the item is unknown, the field will be marked "Unknown."

Prior to the start of the study, the Principal Investigator will complete a Delegation of Authority form (Site Signature and Delegation Log), showing the signatures and handwritten initials of all individuals and the delegation of responsibilities, such as identifying those individuals who are authorized to make or change entries on eCRFs

19.2. Case Report Form Completion

Data within the eCRF will be monitored by the Clinical Research Associate according to the Monitoring Plan. Queries will be generated based on discrepancies found while monitoring. Site personnel will review and respond to these queries appropriately. Additionally, the Sponsor's designee and the Sponsor may periodically perform aggregate data reviews, which could result in queries being generated for site personnel resolution. The final, completed eCRF for each patient must be signed and dated by the Principal Investigator to signify that the Principal Investigator has reviewed the eCRF and certifies it to be complete and accurate.

19.3. Database Management, Data Clarification, and Quality Assurance

The Sponsor's designee, ie, a designated CRO, will be responsible for data management. Data Management will develop a data management plan (DMP) document, and provide it to the Sponsor for approval. The DMP document will define all activities in the data collection and cleaning process. The detailed DMP will be based on the protocol, work scope, contract, analysis plans, data flows, eCRFs, data cleaning procedures, other supporting documents, and data management standards and practices.

The programmed data validations will be run to check for database completeness and consistency, and queries will be generated upon data entry or via review by a Clinical Data Manager after entry. The sites will respond to the data queries in a timely manner.

Concurrent medications entered into the database will be coded using a WHO dictionary. Coexistent diseases and AEs will be coded using MedDRA.

Quality control procedures will be conducted prior to database lock according to the designated CRO SOPs.

When the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time will only be made by joint written agreement between the Sponsor, the trial statistician, the data manager, and the quality assurance auditor, according to designated CRO SOPs.

19.4. Inspection of Records/Source Documents

According to the ICH guidelines for GCP, the Sponsor or designee must verify data entered in the eCRF entries against the source documents, except for the pre-identified source data directly documented in the eCRF (if applicable). The ICF will include a statement by which the patient allows the sponsor's duly authorized personnel, the IRB or EC, and the regulatory authorities to have direct access to source data that supports the data in the eCRF (eg, patient's medical file, appointment books, and original laboratory records). These personnel, bound by professional secrecy, must keep confidential all personal medical information.

The objective of source document verification (SDV) is to comply with GCP and international regulatory requirements and to reduce the risks of fraud. Source Document Verification means ensuring that the source documents are an accurate and verifiable reflection of the patient's participation in the study and that all relevant information that is recorded in the source document is accurately entered into the eCRF.

Where source documents serve as the basis for deriving data for the trial, SDV should ensure that these documents are correctly labeled and filed and that the data derived from them are correct.

All data required for this study should be captured in source notes. No data obtained by the Investigator or other study personnel should be captured directly in the eCRF. All source documents pertaining to this study will be maintained by the Investigator and made available for inspection by authorized persons. If electronic progress notes and other electronic source documents are not Title 21 CFR Part 11 compliant, they are not considered a valid source for this study. All progress notes must be dated and signed by the Principal Investigator or Sub-Investigator at the time of the visit. The Sponsor reserves the right to terminate the study for refusal of the Investigator to supply original source documentation for this clinical study.

The Investigator will note in a source independent from the eCRF the following information:

1. Information to confirm that the patient exists (eg, initials, date of birth, sex)
2. Confirmation that the patient satisfies the inclusion/exclusion criteria
3. Confirmation that the patient is taking part in the clinical trial
4. Confirmation of the informed consent process
5. Visit dates and documentation of protocol assessments and procedures
6. Information concerning all AEs
7. Details of concomitant and investigational medications.

Source Document Verification is not a substitute for clinical trial monitoring, the purpose of which is to ensure that the protocol has been followed correctly, the eCRF has been fully and

accurately completed, SDV has been carried out, and the study timelines and enrollment goals and requirements have been met.

19.5. Retention of Records

In the United States, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

The Investigator must take measures to prevent accidental or premature destruction of these documents.

The Investigator must notify the Sponsor prior to destroying any study essential documents.

If the Investigator can no longer ensure archiving, he/she shall inform the Sponsor. The relevant records shall be transferred to a mutually agreed-upon designee.

21. REFERENCES

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22. APPENDICES

APPENDIX A. LABORATORY ASSESSMENTS

HEMATOLOGY	CLINICAL CHEMISTRY	URINALYSIS
Complete blood count (CBC) Platelet count White blood cell (WBC) count with differential	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	Bilirubin Glucose Ketones Nitrates Occult Blood Protein Specific gravity Urobilinogen pH Leukocytes Microscopic urine analysis if dipstick positive **LFTs** Total bilirubin Direct bilirubin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Gamma-glutamyl transferase Total serum protein
SEROLOGY SCREEN	**COAGULATION**	**PREGNANCY**
Hepatitis B surface antigen (HBsAg) Hepatitis C virus antibody (HCV-Ab)	Prothrombin Time Test (PT) Partial Prothrombin Time Test (aPTT) International normalized ratio (INR)	Human chorionic gonadotropin (hCG)

APPENDIX B. CYTOCHROME P450 DRUG INTERACTIONS

CYP P450 3A4/3A5/3A7 Inhibitors:	CYP P450 3A4/3A5Inducers:
• 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