1. Title Page

CLINICAL STUDY PROTOCOL

PHASE 1B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE ESCALATION STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF QR-010 IN SUBJECTS WITH HOMOZYGOUS ΔF508 CYSTIC FIBROSIS

Protocol No.	PQ-010-001
Protocol/Amendment Date:	04 April 2017
Protocol/Amendment No.:	20
Protocol Version:	8.0
Supersedes:	7.0, 7.1, 7.2
EudraCT/IND Number	2014-004352-57/120893
Sponsor:	ProQR Therapeutics Zernikedreef 9 2333 CK Leiden The Netherlands
Sponsor Chief Development Officer and Study Medical Monitor: **Telephone Number:**	[redacted]

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INVESTIGATOR SIGNATURE PAGE

ProQR Therapeutics

Protocol No. PQ-010-001, Version No. 8.0
04 April 2017

PRINCIPAL INVESTIGATOR COMMITMENT:

I will provide copies of the protocol, any subsequent protocol amendments and access to all information provided by the Sponsor to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the study protocol.

I agree to conduct this clinical trial according to the attached protocol, except when mutually agreed to in writing. I also agree to conduct this study in compliance with all federal, state and local regulations, Good Clinical Practices (GCP), as well as with the requirements of the appropriate Institutional Review Board(s) (IRB)/Ethics Committee(s) (EC) and any other institutional requirements.

_____

Printed Name of Principal Investigator

_____

Signature of Principal Investigator

_____

Date

_____

Institution

_____

Address of Institution

PROTOCOL APPROVAL PAGE

Phase 1b, Randomized, Double-blind, Placebo-controlled, Dose Escalation Study to Evaluate the Safety, Tolerability and Pharmacokinetics of QR-010 in Subjects With Homozygous ΔF508 Cystic Fibrosis

Protocol No.	PQ-010-001
Protocol/Amendment Date:	04 April 2017
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Protocol Version:	8.0

SPONSOR: **ProQR Therapeutics**
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04 April 2017

Date

NATIONAL COORDINATING INVESTIGATORS

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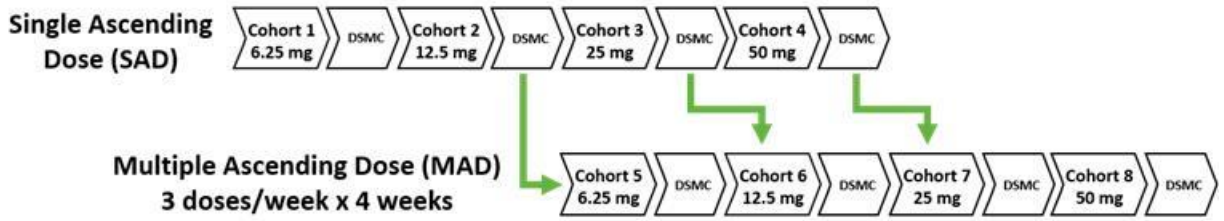
Name **Institution** **Street Address** **City, Country, Postal Code**	

1.0 SYNOPSIS

Name of Sponsor/Company: ProQR Therapeutics	**Individual Study Table Referring to Part of the Dossier** **Volume:** NA **Page:** NA	*(For National Authority Use only)*
Name of Investigational Product: QR-010 Solution for Nebulization		
Name of Active Ingredient: QR-010		
Title of Study:	Phase 1b, Randomized, Double-blind, Placebo-controlled, Dose Escalation Study to Evaluate the Safety, Tolerability and Pharmacokinetics of QR-010 in Subjects With Homozygous ΔF508 Cystic Fibrosis	
Investigators:	To be determined	
Study Centers:	Approximately 27 centers in North America and European Union (EU)	
Phase of Development:	1b	
Study Period:	24 months	
Duration of Subject Participation:	9 days (single ascending dose cohorts) 8 weeks (multiple ascending dose cohorts)	
Objectives:	Primary: To evaluate the safety and tolerability of QR-010 administered via inhalation and identify the maximum tolerated dose (MTD). Secondary: To evaluate the change from baseline analysis for laboratory parameters and vital signs as well as the pharmacokinetics (PK) of QR-010 administered via inhalation. Exploratory: To explore the efficacy of QR-010 administered via inhalation.	
Study Design:	Randomized, double-blind (investigator and subject), placebo-controlled, single ascending and multiple ascending dose-escalation study. This study includes two portions: four single ascending dose (SAD) cohorts (1-4) and four multiple ascending dose (MAD) cohorts (5-8). An independent Data Safety Monitoring Committee (DSMC) will be designated to review all safety data at the end of each cohort. Safety data will include 7 days of follow up after the dose administered for SAD cohort subjects, and 7 days after the last dose administered for MAD cohort subjects. Initiation of the first MAD dose cohort will be based on the determination of the DSMC that an adequate safety profile has been demonstrated in the first two SAD cohorts. Similarly, subsequent MAD dosing cohorts will be initiated based on the determination of the DSMC that an adequate safety profile is demonstrated in the corresponding supportive SAD and MAD cohorts. Lastly, the DSMC will review safety data on an ad hoc basis. The type of adverse event (AE) that would trigger such an ad hoc DSMC review would be documented in the data safety monitoring plan.	



Number of Subjects (planned):	Approximately 32 subjects in each of the SAD and MAD portions will be enrolled in the study, with 8 subjects per cohort, randomized at a 3:1 ratio (6 active and 2 placebo), for a total of 64 subjects in the study. The exact number of subjects enrolled is dependent on whether any dose levels are to be expanded due to the occurrence of dose-limiting toxicities (DLTs).
Diagnosis and Main Criteria for Eligibility:	Inclusion Criteria: 1. Able and willing to comply with the protocol and provide written informed consent prior to study-specific screening procedures 2. Able and willing to adequately and consistently perform spirometry as required by the protocol 3. Able and willing to participate in standardized airway clearance techniques 4. Confirmed diagnosis of CF as defined by iontophoretic pilocarpine sweat chloride test (sweat chloride) of > 60 mmol/L 5. Confirmation of cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations homozygous for the ΔF508 mutation. Genetic testing performed prior to the year 2000 must be re-confirmed. 6. Male or female 18 to 60 years of age 7. Body mass index (BMI) of ≥ 17 kg/m^2 8. Non-smoking for a minimum of two years, including cigarettes, cigars, and e-cigarettes 9. Stable pulmonary symptoms associated with CF 10. Creatinine Clearance > 60 mL/min, as calculated by Cockcroft-Gault equation based on actual body weight 11A. Women of childbearing potential must agree to use a highly effective method of birth control (defined as those, alone or in combination, that result in a low failure rate [ie, less than 1% per year]). See Section 6.3.3 for a list of highly effective methods of birth control. 11B. Men must agree to use barrier contraception (ie, condoms) except when infertility is documented (eg, bilateral orchidectomy or azospermia and/or infertility secondary to CF) 12. FEV_1 ≥ 70% of predicted normal for age, gender, and height (post-bronchodilator value using NHANES III standards) at screening 13. Stable lung function determined by the treating physician, provided FEV_1 at Day -1 is within 10% of FEV_1 at screening NOTE: Eligibility criteria 14 through 20 relate to acceptable laboratory values at screening. Subjects with a screening laboratory value outside the specified range may be permitted if the value is not clinically significant in the opinion of the Investigator, with concurrence from the Sponsor's Medical Monitor. 14. Total WBC ≤ 12,000/μL

	15. Hemoglobin > 10 g/dL 16. Hematocrit > 30% 17. Platelet count between 150 and 450 x $10^3/\mu L$ 18. Prothrombin time, international normalized ratio (INR) and partial thromboplastin time within normal limits 19. Serum albumin > 2.5 g/dL at screening 20. Liver function tests within 2X the upper limit of normal (SGPT/ALT, SGOT/AST, GGT, alkaline phosphatase, bilirubin [total and direct]) <u>Exclusion Criteria</u>: 1. Personal or family history of prolonged QT syndrome; or a QTc interval > 430 msec (males) or > 450 msec (females) using Bazett's formula (QTcB) 2. Change in body weight within 90 days prior to Day 1 that is considered clinically significant by the Investigator 3. Abnormal vital signs at screening: heart rate > 120 bpm at rest; systolic blood pressure > 140 or < 90 mmHg; respiration rate > 24 bpm; and SpO2 < 92% at rest 4. History of alcohol abuse within the past 24 months or positive drug test at screening. Presence of drug(s) administered for known conditions are permitted with concurrence from the Sponsor's Medical Monitor (eg, benzodiazepine, oral cannabis). 5. Any infection including acute upper respiratory or lower respiratory infections, pulmonary exacerbation, changes in therapy for pulmonary disease, or any non CF-related illness which results in the initiation of any new therapy within 30 days prior to Day 1 6. Clinically significant, abnormal screening laboratory value (as determined by the Investigator) or any abnormal screening laboratory value that would place the subject at undue risk while participating in the study (as determined by the Investigator with concurrence from the Sponsor's Medical Monitor) 7. Breast-feeding or pregnant female 8. Significant change in maintenance medications for CF within 30 days of Day 1 9. Use of lumacaftor or ivacaftor within 45 days of Day 1 10. Use of any investigational drug (other than QR-010) or device within 30 days of Day 1 11. Unable to or unwilling to perform key safety evaluations such as spirometry 12. Unable to participate in standardized airway clearance techniques 13. Presence or medical history of clinically significant disease which precludes study participation or prevents determination of outcome measures 14. History of lung transplantation 15. Hemoptysis of greater than 30 mLs within 90 days prior to Day 1, or hospitalization for hemoptysis within 6 months of Day 1 16. Any severe, acute, or chronic medical or psychiatric condition, laboratory abnormality, or other condition that, in the judgment of the Investigator, would place the subject at undue risk, interfere with the results of the study or make the subject otherwise unsuitable

	17. Any difficulty complying with protocol requirements that may increase the risk associated with study participation or study drug administration or may interfere with safety
Test Product, Dosage and Mode of Administration:	QR-010 Solution for Nebulization, 50 mg/mL (2 mL/vial) in isotonic sodium chloride solution, Inhalation via nebulizer. SAD cohorts: 6.25, 12.5, 25, or 50 mg, once per subject. MAD cohorts: 6.25, 12.5, 25, or 50 mg, thrice weekly for 4 weeks, for a total of 12 doses per subject.
Duration of Treatment:	Cohorts 1-4: 1 day Cohorts 5-8**:** 4 weeks
Reference Therapy, Dosage and Mode of Administration:	Placebo Solution for Nebulization, 0.9% sodium chloride solution, Inhalation via nebulizer. Placebo in the SAD will be administered once. Placebo in the MAD will be administered thrice weekly for 4 weeks, for a total of 12 doses per subject.
Criteria for Evaluation:	
Safety and Tolerability:	Safety will be assessed by monitoring AEs, vital signs, laboratory data (chemistries, hematology and urinalysis), immunogenicity evaluation, ECGs, pulmonary function, and physical examinations. • Adverse events (AEs) • Physical examination (PE) at screening, baseline and end of study • Vital signs • Electrocardiograms (ECGs) at screening, baseline and end of study • Continuous cardiac monitoring (telemetry) • Spirometry (FEV_1) at baseline, 10, 30, and 60 minutes, and 2, 4, and 8 hours post-dose following the first dose to evaluate for provoked bronchospasm • Chest radiograph at screening and end of treatment (MAD only) • Laboratory analysis for signs of toxicity: hepatic, renal, immunogenicity
PK:	Subjects will provide blood, urine and expectorated sputum samples for presence of QR-010 at multiple time points.
Exploratory Safety and Efficacy:	The following will be performed or collected for exploratory evaluation and analysis: • Blood (serum and plasma) and expectorated sputum for inflammatory biomarkers • Spirometry (FEV_1) baseline, weekly during dosing, end of study, and at the follow-up visits (MAD Cohorts only) • Cystic Fibrosis Questionnaire-Revised Respiratory Symptom Score (CFQ-R RSS) at baseline, prior to dose 7, and end of treatment (MAD Cohorts only) • Sweat chloride determination by pilocarpine iontophoresis at screening (all cohorts), on the last dosing day, and at follow-up visits 7 and 8 days after last dose (MAD cohorts only)

	• Body weight at baseline, and throughout the study • Sputum microbiology at baseline and end of study for SAD cohorts, and at the End of Treatment Visit for MAD cohorts
Statistical Methods:	Baseline safety and exploratory endpoints will be summarized descriptively for SAD and MAD separately. No inferential testing will be performed. Serum concentrations of QR-010 will be summarised by dose level and time point. Individual concentration-time graphs will be presented. Graphs of mean concentration over time, for each dose, will also be presented. Summary statistics for AUC, C_{max}, T_{max}, $t_{1/2}$, and dose-normalized AUC and C_{max} will be presented by dose level. Graphs of AUC and Cmax versus dose will be displayed. Dose proportionality may be explored using analysis of variance (ANOVA) on log-transformed and dose normalized C_{max} and AUC parameters, if there are sufficient data to support the analysis. Additionally, the power approach could be used to investigate for dose proportionality. Any p values that will be calculated according to the analysis plan will be interpreted in view of the exploratory nature of the study.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition/Explanation
ADL	Activities of Daily Living
AE	Adverse Event
ALT (SGPT)	Alanine aminotransferase (Serum Glutamic Pyruvic Transaminase)
ANOVA	Analysis of Variance
AON	Antisense Oligonucleotide
AST (SGOT)	Aspartate aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
ATP	Adenosine triphosphate
ATS	American Thoracic Society
AUC	Area Under the Curve
$AUC_{0-\infty}$	Area under the curve from time zero to infinity
AUC_{0-t}	Area under the curve from time zero to the final time point
bpm	Beats per minute; Breaths per minute
bps	Base pairs
BUN	Blood Urea Nitrogen
C	Celsius
CBC	Complete Blood Count
CF	Cystic Fibrosis
CFR	Code of Federal Regulations
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFQ-R RSS	Cystic Fibrosis Questionnaire-Revised Respiratory Symptoms Score
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CH50	Total Complement
CL	Serum Clearance
Clinically significant	An abnormal finding/laboratory value that indicates a new disease process, an exacerbation or worsening of an existing condition, or requires further action(s) to be taken (eg, initiation of new therapy).
C_{max}	Maximum Concentration
C_{min}	Minimum Concentration
CRF, eCRF	Case Report Form, Electronic Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	Clinical Study Report

Abbreviation or Term	Definition/Explanation
CTCAE	Common Terminology Criteria for Adverse Events
CXR	Chest Xray
DAT	Direct Antiglobulin Test
dL	Deciliter
DLT	Dose–Limiting Toxicity
DP	Drug Product
DS	Drug Substance
DSMC	Data Safety Monitoring Committee
EC, IEC	Ethics Committee, Independent Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
ENaC	Epithelial Sodium Channel
ERS	European Respiratory Society
ESR	Erythrocyte Sedimentation Rate
ET	Early Termination
EU	European Union
F	Fahrenheit
FDA	Food and Drug Administration
FEF_{25-75}	Forced Expiratory Flow between 25 and 75% of the FVC
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
g	Gram
GCP	Good Clinical Practice
Hct	Hematocrit
HED	Human Equivalent Dose
Hgb	Hemoglobin
HHS	Health and Human Services
HIPAA	Health Information Portability and Accountability Act of 1996
HR	Heart Rate
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IRB	Institutional Review Board

Abbreviation or Term	Definition/Explanation
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IWRS	Interactive web response system
kg	Kilogram
L	Liter
LABA	Long-acting β-agonist
LDH	Lactic Dehydrogenase
LLQ	Lower Limit of Quantitation
MAD	Multiple Ascending Dose
MDD	Maximum Deliverable Dose
mRNA	Messenger Ribonucleic Acid
µg	Microgram
mg	Milligram
mL	Milliliter
mmHg	Millimeters of Mercury
MRSD	Maximum Recommended Starting Dose
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
N	Normal
ng	Nanogram
NOAEL	No Adverse Effect Level
NPD	Nasal Potential Difference
OTC	Over the Counter
PCL	Periciliary Layer
PD	Pharmacodynamics
PDD	Pulmonary Deposited Dose
PE	Physical examination
pH	Hydrogen ion concentration
PK	Pharmacokinetics
POC	Proof of Concept
Post	After

Abbreviation or Term	Definition/Explanation
Pre	Before
PS	Phosphorothioate
PT	Prothrombin Time, Preferred Term
PTT	Partial Thromboplastin Time
QTc	QT Interval-Corrected
RBC	Red Blood Cell
RNA	Ribonucleic Acid
SABA	Short-acting β-agonist
SAD	Single Ascending Dose
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SGOT (AST)	Serum Glutamic Oxaloacetic Transaminase
SGPT (ALT)	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal elimination phase half-life
TEAE	Treatment-Emergent Adverse Event
tiw	Thrice Weekly (three times per week)
TK	Toxicokinetic
TLF	Tables, Listings and Figures
t_{max}	Time to maximum concentration
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WT	Wild Type

2.0 INTRODUCTION

ProQR Therapeutics (ProQR, the Sponsor) is developing an antisense oligonucleotide (AON) product, QR-010, for the chronic treatment of patients with cystic fibrosis (CF) that is associated with either a compound hetero- or homozygous genotype for the absence of phenylalanine at position 508 (ΔF508/p.Phe508del) on cystic fibrosis transmembrane conductance regulator (CFTR)-encoded ribonucleic acid (RNA). QR-010 is a single-stranded RNA oligonucleotide that is complementary to the ΔF508 region on the RNA transcription product of the CFTR gene. Translation of the repaired CFTR encoded RNA should result in [redacted] normal CFTR protein. The intended route of clinical administration is oral inhalation (inhalation) of nebulized QR-010 solution.

Cystic Fibrosis Associated with ΔF508 CFTR Genotype

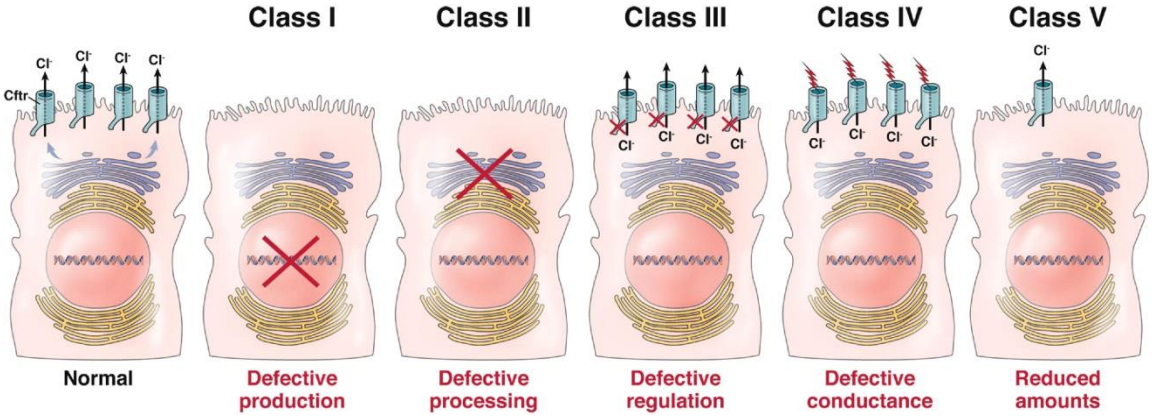
Cystic fibrosis is an autosomal recessive disorder that is caused by a mutation in a gene that encodes CFTR, a membrane protein with pleiotropic functions. CFTR regulates the surface liquid layer and is found in the epithelial cells of the respiratory, gastrointestinal, and biliary systems; male reproductive tract; and exocrine sweat glands. This protein consists of 1480 amino acids that are divided into five domains, two of which cross the membrane to form a bidirectional, trans-membrane chloride channel (Riordan *et al.*, 1989). Although CFTR functions primarily as a chloride channel, it has many other regulatory roles that affect the CF phenotype. These include inhibition of sodium transport through the epithelial sodium channel (ENaC), regulation of the outwardly rectifying chloride channel, regulation of adenosine triphosphate (ATP) channels, regulation of intracellular vesicle transport, acidification of intracellular organelles, and inhibition of endogenous calcium-activated chloride channels. The CFTR protein is also involved in bicarbonate–chloride exchange. A deficiency in bicarbonate secretion leads to poor solubility and aggregation of luminal mucins. Lack of CFTR function results in the multi-organ system clinical syndromes described in patients with CF (Collawn *et al.*, 2012; Mehta , 2005; O'Sullivan & Freedman, 2009; Quinton , 1999; Reisin *et al.*, 1994; Vankeerberghen *et al.*, 2002).

The CFTR gene is encoded on chromosome 7 (Chr 7 117,120,017 through to 117,308,715). The transcription product of the CFTR gene (189 kb) is a messenger RNA (mRNA) (6.1 kb) that is translated into the CFTR protein. A patient with a CF phenotype has a CFTR gene mutation on both alleles and may be homozygous for a single mutation or compound heterozygous with a different mutation on each allele. There are nearly 2000 CFTR gene variants. However, only 159 variants have an allele frequency ≥ 0.01% and 127 of those 159 variants meet both the clinical (pilocarpine iontophoresis sweat chloride test) and functional (affects RNA quality/quantity or CFTR protein) criteria to cause CF. Together, these 159 variants account for 96.4% of identified cystic fibrosis alleles. The ΔF508 mutation is the most common allelic mutation and accounts for about 66-70% of identified mutated alleles in northern European and North American populations. According to the Cystic Fibrosis Foundation National Patient Registry Annual Data Report (2012), a total of 23,053 CF patients (86.7% of the CF population in the US) in the US

had one or two copies of the ΔF508 mutation (O'Sullivan & Freedman, 2009; Sosnay*et al.*, 2013).

The various CFTR mutations are often classified into 5 specific functional classes, as shown in Figure 1. The ΔF508 mutation (hetero- or homozygous) is a Class II CFTR functional mutation that is characterized by defective CFTR processing; the gene is transcribed but the translated protein product is not trafficked through the endoplasmic reticulum and is degraded before reaching the cell surface. The ΔF508 mutation results in a CFTR protein that is mis-folded, which results in ubiquination and degradation. As a result, little, if any, CFTR reaches the plasma membrane. QR-010 has the potential to treat all CF patients with the ΔF508 mutation on at least one allele (O'Sullivan & Freedman, 2009; Pasyk & Foskett, 1995; Zamecnik *et al.*, 2004).

Figure 1: Classes of CFTR Mutations



Classes of CFTR mutations. Categories of CFTR mutations with mutations resulting in no synthesis (Class I), defective processing (Class II), defective regulation (Class III), defective or deficient conductance (Class IV), and reduced amount of functional CFTR protein (Class V).

Source: Gelfond & Borowitz, 2013

The most common cause of death in patients with CF is respiratory failure due to progressive loss of lung function and/or pulmonary disease (Davies *et al*., 2007). There are several hypotheses regarding the mechanism by which the ΔF508 mutation leads to the multi-organ system CF phenotype and progressive loss of function, however the causal relationship between CFTR dysfunction and the CF phenotype is well established (Sosnay, 2013). In the simplest pathophysiological scenario, functional CFTR is either absent or substantially reduced at the apical membrane; the absence of functional CFTR at the apical membrane of ciliated airway epithelial cells of the respiratory tract results in a reduced capacity to secrete chloride ions to the airway surface and, indirectly, in an increased absorption of sodium ions from airway surfaces (Collawn *et al.*, 2012; O'Sullivan & Freedman, 2009). This imbalance of active ion transport favors the net removal of salt and concomitant water from airway surfaces. Loss of water in the gel-like periciliary layer results in a loss of lubrication of the airway surface and increased concentrations of mucin in the mucus layer. Dehydrated periciliary layer (PCL) leads to thicker mucus and cilia collapse, which results in a reduced mucociliary clearance. The 'stuck' mucus

ultimately creates an adhesive plaque, or 'mucus plug'. These plaques stimulate inflammation, obstruct the airway lumen, produce airflow obstruction, and serve as a nidus for persistent bacterial infections. It is the same loss of CFTR-mediated ion regulation that leads to dysfunction in other organ systems, including the gastrointestinal (eg, malabsorption), biliary, pancreatic and sweat exocrine, reproductive (congenital bilateral absence of the vas deferens in males) systems.

QR-010 Product Description

QR-010 is under development for the chronic treatment of patients with CF that is associated with either a compound hetero- or homozygous genotype for the absence of ΔF508 on CFTR-encoded RNA. The goal of treatment with QR-010 is repair of the CFTR region of the RNA encoded with the ΔF508 mutation. Translation of the repaired CFTR encoded RNA should result in [redacted] normal CFTR protein. The intended route of clinical administration is inhalation of nebulized QR-010 solution, which is anticipated to result in both local effects to the respiratory system and systemic absorption. Hence, QR-010 has the potential to treat both pulmonary and extra-pulmonary manifestations of CF.

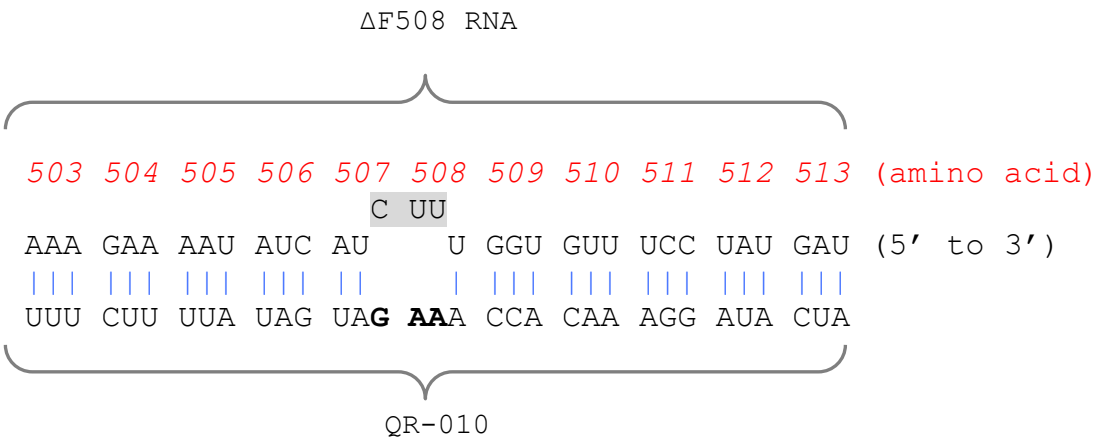
QR-010 was developed from a synthetic RNA oligonucleotide duplex that was described in a 2004 paper by Dr. Paul Zamecnik, a pioneer of antisense therapeutics (Stephenson & Zamecnik, 1978, Zamecnik & Stephenson, 1978, Zamecnik *et al.*, 1986, Zamecnik *et al.*, 2004). [redacted] The Sponsor's product development program explored various chemical modifications to the original molecule to optimize function (ability to restore CFTR activity [redacted]) in vitro and cellular uptake in vivo. The molecule selected for further development, QR-010, is a single-stranded, 33-mer RNA oligonucleotide with 2'O-Me base modifications and a full phosphorothioate (PS) backbone. QR-010 is highly specific for the CFTR RNA, with 14 and 16 complementary base-pairs on either side of the ΔF508 deletion region, as confirmed using the basic local alignment search tool (BLAST) at the National Center for Biotechnology Information (search most-recently conducted 21 August 2014)[1].

As described above, QR-010 is a single-stranded 33-mer RNA oligonucleotide with 2'O-Me base modifications and a full PS backbone. QR-010 is highly specific for the CFTR RNA, with 14 complementary base pairs (bps) on the 5' side and 16 complementary bps on the 3' side of the ΔF508 deletion region. To address the question of whether or not QR-010 was specific to this region of the CFTR RNA, a basic local alignment search tool (BLAST) at the National Center for Biotechnology Information was conducted and showed 100% specificity for this region. Repeated BLAST searches were completed, with the most recent conducted 21 August 2014.

[1] Available at http://blast.ncbi.nlm.nih.gov/Blast.cgi

Figure 2 illustrates the sequence that contains the ΔF508 mutation and the complementary hybridization of QR-010 to that region.

Figure 2: Hybridization of QR-010 to the ΔF508-CFTR RNA



Sequence with grey shading (C-U-U) on ΔF508 RNA represents the absence of phenylalanine at position 508 (ΔF508 mutation). Because both A-U-C (wild-type) and A-U-U (ΔF508) code for isoleucine, position 507's amino acid is unchanged, and the net effect of the 3 nucleotides missing in the ΔF508 mutation is omission of a phenylalanine ("F") at position 508 in the translated protein. Vertical bars represent the QR-010 binding region. Bold text (G-A-A) on QR-010 represents the complement of the missing C-U-U sequence.

2.1 Background

2.1.1 Description of Drug Substance (Active Pharmaceutical Ingredient)

QR-010 Drug Substance (DS) is a white to off-white lyophilized powder. It is an anhydrous sodium salt with molecular formula $C_{347}H_{420}N_{122}Na_{32}O_{195}P_{32}S_{32}$ and molecular mass of 12172.66 Daltons. QR-010 DS is stable at ambient temperature but undergoes some degradation when exposed to 80°C and significant degradation when exposed to oxidative stress (0.3% H_2O_2 solution).

2.1.2 Description of Drug Product

2.1.2.1 Drug Product

QR-010 Drug Product (DP) is a solution for nebulization presented in a Type I glass vial containing a clear, colorless solution available at a concentration of 50 mg/mL (2 mL/vial) in 0.7% sodium chloride solution. The DP has a pH between 6.0 and 8.0, and osmolality equal to 0.9% sodium chloride solution. QR-010 DP is labeled with the appropriate information as specified in the clinical protocol and as necessitated by local regulatory requirements. Throughout the document the name used for the DP is: QR-010 Solution for Nebulization.

The eFlow® Nebulizer System [redacted] will be used for study drug administration in the European Union (EU). The Investigational eFlow® Nebulizer System [redacted] will be used for study drug administration in North America. These devices are identical and will be referred to as eFlow in this protocol.

2.1.2.2 Placebo

Placebo, QR-010 Placebo Solution for Nebulization, is a solution of 0.9% sodium chloride. It is similar to QR-010 Solution for Nebulization except the active ingredient, QR-010, is excluded. The placebo is labeled with the appropriate information as specified in the clinical protocol and as necessitated by local regulatory requirements.

2.1.3 Nonclinical

The nonclinical pharmacology program investigated QR-010 using both in vitro (human cell line and primary cells) and in vivo (mice, Cynomolgus monkeys) systems. The nonclinical pharmacodynamics data demonstrated the inhalation of QR-010 in mice and supported the proposed mechanism of action of treatment with QR-010 in facilitating the phenotypic reversion of ΔF508 CFTR activity to [redacted] CFTR activity. These studies are summarized in QR-010 Investigator's Brochure, Section 5.2 - Nonclinical Pharmacology.

Three preliminary studies contributed bio-distribution data for QR-010. These analyses were conducted in mouse variant C57BL/6J (considered wild-type [WT] for the purposes of these studies). One additional 28-day, repeat-dose GLP-compliant toxicity study in Cynomolgus monkeys provided toxicokinetic (TK) data. These studies are summarized in QR-010 Investigator's Brochure, Section 5.3 - Pharmacokinetics and Product Metabolism in Animals.

The nonclinical toxicology program for QR-010 was conducted in accordance with the following guidelines:

- ICH M3 (R2): *Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*
- ICH S4 Guidance: *Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing)*
- ICH S3A Guidance*: The Assessment of Systemic Exposure in Toxicity Studies*

A total of seven toxicity studies in mice and Cynomolgus monkeys contributed relevant data for the determination of safety and maximum recommended starting dose. These studies are summarized in QR-010 Investigator's Brochure, Section 5.4 – Toxicology.

2.1.4 Clinical Experience

No clinical studies have been conducted with QR-010 Solution for Nebulization.

2.2 Study Rationale

A patient with a CF phenotype has a CFTR gene mutation on *both* alleles and may be homozygous for a single mutation or compound heterozygous with a different mutation on each allele. There are nearly 2000 CFTR gene variants. However, only 159 variants have an allele frequency ≥ 0.01% and 127 of those 159 variants meet both the clinical (sweat chloride test) and functional (affects RNA quality/quantity or CFTR protein) criteria to cause CF. Together, these 159 variants account for 96.4% of identified cystic fibrosis alleles. The ΔF508 mutation is the most common allelic mutation and accounts for about 66-70% of identified mutated alleles in northern European and North American populations. According to the Cystic Fibrosis Foundation National Patient Registry Annual Data Report (2012), a total of 23,053 CF patients (86.7% of the CF population in the US) in the US had one or two copies of the ΔF508 mutation (O'Sullivan & Freedman, 2009; Sosnay, *et al.*, 2013).

The ΔF508 mutation (hetero- or homozygous) is a Class II CFTR functional mutation that is characterized by defective CFTR processing; the gene is transcribed but the translated protein product is not trafficked through the endoplasmic reticulum and is degraded before reaching the cell surface. The ΔF508 mutation results in a CFTR protein that is mis-folded, which results in ubiquination and degradation. As a result, little, if any, CFTR reaches the plasma membrane. The absence of functional CFTR at the apical membrane of ciliated airway epithelial cells of the respiratory tract results in loss of CFTR-mediated ion regulation, which ultimately results in airway inflammation, obstruction, and persistant bacterial infections (Collawn *et al.*, 2012; O'Sullivan & Freedman, 2009). It is the same loss of CFTR-mediated ion regulation that leads to dysfunction in other organ systems, including the gastrointestinal (eg, malabsorption), biliary, pancreatic and sweat exocrine, reproductive (congenital bilateral absence of the vas deferens in males) systems.

Although many organ systems are affected in CF, the most common cause of death is respiratory failure due to progressive loss of lung function and/or pulmonary disease (Davies *et al*., 2007). Hence, patients with CF would greatly benefit from a therapy targeted to the respiratory system that facilitated the phenotypic reversion of ΔF508 CFTR activity to [redacted] normal CFTR activity. Worldwide, there is no marketed therapy that facilitates repair of the CFTR protein by targeting the RNA transcription product of the CFTR gene.

QR-010 is a single-stranded RNA oligonucleotide that is complementary to the CFTR region on the RNA transcription product of the CFTR gene. Hence, QR-010 has the potential to treat all CF patients with the ΔF508 mutation on at least one allele. The QR-010 nonclinical program demonstrated that QR-010 facilitated the phenotypic reversion of ΔF508 CFTR activity to [redacted] CFTR activity both in mice that were homozygous for the ΔF508 mutation and in cystic fibrosis human cell cultures with the ΔF508 mutation. The QR-010 nonclinical program also demonstrated the inhalation safety and toxicology of QR-010 in WT mice and WT Cynomolgus monkeys. The clinical development program will investigate the long-term safety and efficacy of QR-010 in treating in adult and pediatric patients who exhibit CF phenotypes with varying degrees of disease severity.

The initial clinical study, PQ-010-001, will be a single- and multiple-ascending dose (SAD and MAD, respectively) study that will evaluate safety, tolerability, and the maximum tolerated dose (MTD) of QR-010 Solution for Nebulization in CF patients who are homozygous for the ΔF508 mutation. Exploratory efficacy endpoints are proposed but the study will not be sufficiently powered to test efficacy. Subjects will have baseline lung function defined as $FEV_1 \geq 70\%$ predicted for safety reasons. The Phase 1b study will be conducted in North America and select European countries.

2.2.1 Dose Selection Rationale

Dose selection was based on the human equivalence dose (HED) and maximum recommended starting dose (MRSD) that were derived from 28-day toxicology studies in mouse and Cyanomolgus monkey studies, and further details can be found in the Investigator Brochure.

The doses in the intended dose escalation scheme (6.25, 12.5, 25, and 50 mg) in Study PQ-010-001 correspond to the fill dose (mg loaded into the nebulizer) for the nebulizer. The maximum fill volume of the eFlow, the device that will be used to deliver study medication, is 4 mL. In Study PQ-010-001, the fill volume will be 4 mL for all doses in the dose escalation scheme. The doses will be adjusted by diluting the 50 mg/mL solution. The actual delivered dose of QR-010 Solution for Nebulization using the eFlow with a 4 mL fill is < 80% of the fill dose. Hence, the maximum amount of drug delivered to patients will be approximately 5, 10, 20, and 40 mg under the dose escalation scheme.

The maximum loaded (50 mg) and estimated maximum delivered doses (40 mg) roughly correspond to one-half of the MRSD of 104 mg. In addition, the MRSD incorporated a safety factor of greater than 5 times the pulmonary deposited dose (PDD) (based on data from the 28-day toxicity study that was conducted in Cynomolgus monkeys), and it is expected that there will be a lower bioavailability of QR-010 in the lungs of CF patients. In consideration of all the points above, the proposed dose escalation scheme for PQ-010-001 is considered highly conservative.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of QR-010 administered by inhalation to subjects with homozygous ΔF508 cystic fibrosis, and to identify the maximum tolerated dose (MTD) of QR-010.

3.2 Secondary Objective(s)

The secondary objectives of the study are:

- To evaluate the change from baseline analysis for laboratory and vital signs
- To evaluate the pharmacokinetics (PK) of QR-010 administered by inhalation.

3.3 Exploratory Objective(s)

An additional objective of the study is to explore the clinical efficacy of QR-010 administered via inhalation by FEV_1, Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Symptom Score (RSS), change in body weight, and iontophoretic pilocarpine sweat chloride.

4.0 STUDY OVERVIEW

4.1 Criteria for Evaluation

4.1.1 Primary Endpoint

- Incidence and severity of adverse events (AEs) from baseline through end of study
- Occurrence of dose-limiting toxicities (DLT) in each dose cohort from baseline through end of study

4.1.2 Secondary Endpoint(s)

Safety: Changes from baseline to end of treatment or presence of abnormalities on frequent monitoring in laboratory parameters (chemistry, hematology, sputum microbiology, and urinalysis), vital signs, ECG, spirometry, and physical examinations. A chest radiograph will be obtained at screening and at end of treatment (MAD cohorts).

Pharmacokinetics: The PK of QR-010 will be examined in all stages of the study, from first dose through end of study. Specifically, subjects will provide blood, urine and expectorated sputum samples for PK assessments.

4.1.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints of clinical activity will include FEV_1, the patient reported outcome measure CFQ-R Respiratory Symptom Score (CFQ-R RSS), body weight, and pilocarpine iontophoresis sweat chloride at the end of study compared to baseline, for MAD cohorts.

The study will not be sufficiently powered to determine efficacy of QR-010 in the treatment of CF. However, changes in clinical outcome measures that are associated with CF will be monitored over the course of the study in all MAD cohorts. Observed changes in these well-established measures of CF health may inform design of future studies, and include FEV_1, body weight, change in CFQ-R RSS, and pilocarpine iontophoresis sweat chloride. Data indicating potential immunogenicity of QR-010 and change from baseline in inflammatory biomarkers will also be captured.

4.2 Study Design

The study is a multicenter, randomized, double-blind, and placebo-controlled Phase 1b SAD and MAD design. The subject, investigator, and site personnel (except pharmacist) will be blinded to treatment, while the sponsor will be unblinded. Sponsor personnel will be unblinded to subject

treatments in order to permit real-time interpretation of the safety, pharmacokinetic, and pharmacodynamic data. The site monitor will remain blinded to individual subject treatment allocation until all monitoring of study data has been completed. To minimize the potential for bias, individual subject treatment randomization information will not be released to the investigator or blinded study site personnel until the study database has been locked.

Eligible subjects with homozygous ΔF508 CF will be randomized at a 3:1 ratio to receive either QR-010 or placebo vial oral inhalation (nebulization). This study will be conducted in North America and select European countries.

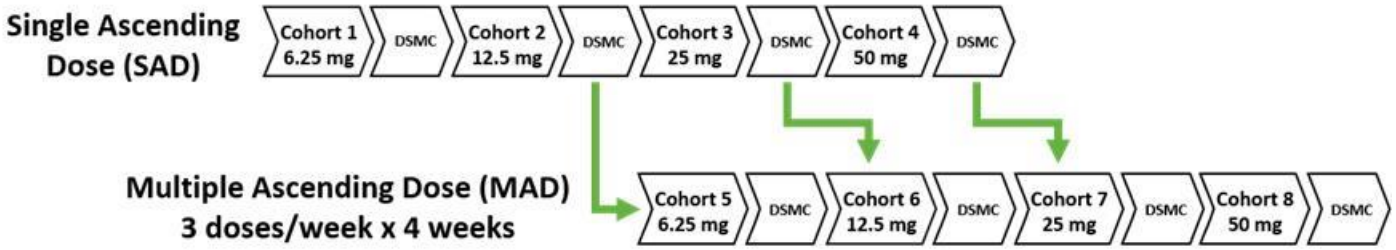
The study includes 2 stages. The first stage is a single ascending dose-escalation (SAD) design to determine safety and tolerability of a single dose of QR-010. The second stage is a multiple ascending dose escalation (MAD) design to further assess the safety, tolerability, and exploratory efficacy of 12 doses of QR-010 over 4 weeks. All doses will be administered in a clinical setting.

For the SAD cohorts, subjects will receive the dose in an inpatient observation unit and be observed for a total 4 days, and will be discharged on Day 4. Subjects will return for PK and safety follow-up as an outpatient on Day 8 (End of Study Visit).

For the MAD cohorts, subjects will receive doses 1 through 12 in a clinic while under observation. On Day 1 and Day 3 subjects will be observed until 12 hours post dose. Following the last dose (dose 12), subjects will return twice for PK sampling, and will be evaluated 7 and 28 days after the last visit for this additional safety monitoring and sampling for PK.

A schematic of the study design is presented in Figure 3.

Figure 3: PQ-010-001 Study Schematic



Single Ascending Dose Escalation Cohorts: The first two subjects of each cohort may be dosed on the same day, at least 4 hours apart. If no significant AEs occur, the remainder of the cohort may be dosed at least 24 hours later, with at least 1 hour between subjects.

After each single dose cohort, an independent Data Safety Monitoring Committee (DSMC) will review available safety data, including 7 days of follow up after administration of QR-010. Dose escalation may occur upon recommendation of the DSMC.

Multiple Ascending Dose Escalation Cohorts: The safety results from the single dose escalation portion of the study will support the initiation of the corresponding multiple dose escalation cohorts, as illustrated in Figure 3.

After each multiple dose cohort, the DSMC will review available safety data, including 7 days of follow up after administration of the last dose of QR-010 (End of Treatment Visit). Dose escalation may occur upon recommendation of the DSMC.

Both Stages: Subjects must sign informed consent before any study-related procedures are initiated. Subjects will receive QR-010 by inhalation via the eFlow device.

Blood, urine and sputum samples will be obtained from all subjects to obtain PK data pre- and post-dosing.

Subjects will undergo clinical and laboratory assessments for safety. Subjects will be withdrawn from the study when intolerable toxicity occurs, or when the subject withdraws consent.

The schedule of assessments is summarized in Appendix 1 and 2.

AE profiles by cohort and dose escalation decisions by the DSMC are communicated to all study sites after DSMC review of cumulative and cohort-specific safety data.

4.3 Dose Escalation

The single dose escalation scheme will test fill doses of 6.25 mg to 50 mg over 4 dose levels, and the multiple dose escalation scheme will test fill doses of 6.25 mg to 50 mg given thrice weekly (tiw) for 4 weeks (Table 1). As described in Section 2.2.1, the dose delivered to subjects via the eFlow device is < 80% of the fill dose, hence the delivered doses that correspond to the dose escalation schemes are shown in Table 1.

Table 1: Dose Escalation

Dose Cohort	Fill Dose (mg)	Estimated Exposure Dose < 80% of Fill Dose (mg)
Single Dose Cohorts		
1	6.25	5
2	12.5	10
3	25	20
4	50	40
Multiple Dose Cohorts (administered tiw for 4 Weeks)		
5	6.25	5
6	12.5	10
7	25	20
8	50	40

tiw = thrice weekly (three times per week)

Dose escalation will initially proceed in single subject cohorts from fill dose level 1 (6.25 mg) to fill dose level 4 (50 mg).

Initiation of MAD Cohort 5 will be based on the safety profile of SAD Cohort 2. Initiation of Cohort 6 will be based on the safety profiles of Cohorts 3 and 5. Similarly, initiation of Cohort 7 will be based on the safety profiles of Cohorts 4 and 6, and finally, the initiation of Cohort 8 will be based on the safety profile of Cohort 7. The first dose between subjects in each cohort must be separated by a minimum of 4 hours.

For the single dose cohorts 1 to 4, dose escalation to the next cohort may occur upon recommendation of the DSMC after the subjects have been observed for at least 7 days and no DLTs have occurred or, if a DLT has occurred, per the dose escalation rules in Section 4.5. For the multiple dose cohorts 5 to 8, dose escalation to the next cohort may occur upon recommendation of the DSMC after the subjects have been observed for at least 7 days after the last dose (End of Treatment Visit). If a DLT occurs in any cohort, the AEs and DLTs will be reviewed by the Investigator and the DSMC before dosing can continue in that cohort. In addition, if ≥ 2 subjects experience a decrease in absolute FEV_1 of ≥ 15% from baseline in any cohort, the data will be reviewed by the DSMC before dose escalation can continue.

The AEs of Interest listed in Table 2 are AEs commonly seen with inhaled products. If AEs of interest occur at a Grade 2 level or higher in a single subject in a cohort, then an additional 4 subjects will be added to the cohort. Any of the Grade ≥ 2 toxicities shown in Table 2, as well as

any other respiratory AEs reported, will be evaluated and considered when making dose escalation decisions. If no additional subjects experience any Grade ≥ 2 AEs of Interest, dose escalation may proceed (if recommended by the DSMC).

The Investigator will base decisions to de-escalate to a lower dose, hold the dose (delay or skip), or discontinue study drug for an individual subject using the CTCAE (modified for CF) toxicity grades, in consultation and agreement with the Sponsor's Medical Monitor. In addition to the CTCAE (modified for CF) toxicity grades, the Investigator should also review the stopping rules in Section 5.5.3 with regard to decreases in FEV_1.

For the multiple dose cohorts, subjects who experience a DLT (defined in Section 4.4) should be discontinued from study drug (whether or not the event resolves), and the End of Treatment Visit procedures should be conducted. An End of Study Visit should also be conducted 28 days after the last study drug dose.

Table 2: Adverse Events of Interest

Adverse Event of Interest	Symptoms (Grade ≥ 2 per CTCAE or as Specified Below)
Atelectasis	Symptomatic (eg, dyspnea, cough); medical intervention indicated (eg, chest physiotherapy, suctioning); bronchoscopic suctioning
Hypotension	non-urgent medical intervention indicated
Bronchospasm	symptomatic, medical intervention indicated
Liver Function Test Elevation	alanine aminotransferase (ALT) > 3-5 x ULN or aspartate aminotransferase (AST) > 3-5 x ULN **AND** a doubling from the baseline value
Pneumonitis	Symptomatic; medical intervention indicated; limiting instrumental ADL
Crackles	Scattered or focal
Dyspnoea	Shortness of breath with minimal exertion; limiting instrumental ADL
Hypoxia	Decreased oxygen saturation with exercise (eg, pulse oximeter < 88%); intermittent supplemental oxygen

ADL = Activities of Daily Living

4.4 Definition of Dose-Limiting Toxicity (DLT)

A Dose-limiting Toxicity (DLT) is defined as follows:

- Allergic reaction requiring medical intervention
- Acute bronchospasm requiring medical intervention
- Other acute AEs of interest requiring immediate medical intervention

Allergic reactions and acute bronchospasm not requiring intervention (Grade 1) are usually considered subject-specific and are not included in the definition of DLT. In this protocol,

allergic reactions and acute bronchospasm not requiring medical intervention are not included in the DLT definition since such reactions may not be product and dose-specific with QR-010.

4.5 Determination of Maximum Tolerated Dose (MTD)

The MTD is defined as one dose level below the dose level at which 2 subjects receiving QR-010 experience a dose limiting toxicity (DLT) for dose cohorts 1-4 or within the first 4 weeks for dose cohorts 5-8. Dose escalation will occur based on the number of DLTs encountered according to the rules in Table 3, as assessed by the DSMC. Dose escalation will continue until the MTD is reached or the maximum dose included in the study, whichever is lower. With the highest planned fill dose of 50 mg, subject exposure will be approximately < 40 mg (< 80% efficiency of the eFlow including residual volume). For the MTD determination, the fill dose will be used.

Table 3: Dose Escalation Rules

Number of Subjects Receiving QR-010 With a DLT at a Given Dose	Dose-Escalation Decision Rule
0 of 6	Proceed to next dose level
1 of 6	If one serious AE (SAE) or Grade ≥ 2 AE occurs, four additional subjects will be enrolled at the same dose. If no additional subjects experience a similar SAE or Grade ≥ 2 AE in the same organ class, the dose escalation may continue pending review of safety by the DSMC. If ≥ 2 subjects experience similar SAE or Grade ≥ 2 AE of the same organ class, dose escalation is to be stopped, pending review by the DSMC. The preceding dose may be considered the MTD by the DSMC.
≥ 2 of 6	Dose escalation will be stopped. The preceding dose will be considered the MTD.

DLT = dose-limiting toxicity; MTD = maximum tolerated dose (one dose level lower than the dose level at which 2 or more subjects experience a DLT of the same organ class)

5.0 SELECTION OF STUDY POPULATION

5.1 Study Population

Subjects with a diagnosis of CF, homozygous for the ΔF508 CFTR mutation who meet all inclusion and exclusion criteria will be eligible for participation in this study.

5.2 Selection of Subjects

Screening of subjects will be performed within 14 days prior to dosing. Medical history, physical examination and vital signs will be recorded. Subjects will undergo electrocardiogram (ECG), chest Xray (CXR), spirometry, and clinical laboratory safety testing. During the study subjects will be permitted to continue on their chronic medications that are considered standard of care for CF. For subjects using inhaled anti-infective agents, preferably the same therapy and dose should be administered throughout the study period (Refer to Section 6.3.1). Subjects with signs of a pulmonary exacerbation or other acute illness will not be included.

The exact number of subjects needed to complete the study depends on the number of cohorts required to reach the MTD and the number enrolled in each dose-escalation cohort. The number of subjects for each of the single dose and multiple dose escalation cohorts is 8 subjects, for a total of 64 subjects, but could theoretically expand to approximately 96 subjects if there are DLTs that require every dose cohort to be expanded. Subjects will be enrolled at approximately 20 study sites in North America and select European countries.

5.3 Inclusion Criteria

1. Able and willing to comply with the protocol and provide written informed consent prior to study-specific screening procedures
2. Able and willing to adequately and consistently perform spirometry as required by the protocol
3. Able and willing to participate in standardized airway clearance techniques
4. Confirmed diagnosis of CF as defined by iontophoretic pilocarpine sweat chloride test (sweat chloride) of > 60 mmol/L
5. Confirmation of cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations homozygous for the ΔF508 mutation. Genetic testing performed prior to the year 2000 must be re-confirmed.
6. Male or female 18 to 60 years of age
7. Body mass index (BMI) of ≥ 17 kg/m^2
8. Non-smoking for a minimum of two years, including cigarettes, cigars, and e-cigarettes
9. Stable pulmonary symptoms associated with CF
10. Creatinine clearance > 60 mL/min, as calculated by Cockcroft-Gault equation based on actual body weight

11. A. Women of childbearing potential must agree to use a highly effective method of birth control (defined as those, alone or in combination, that result in a low failure rate [ie, less than 1% per year]). See Section 6.3.3 for a list of highly effective methods of birth control.
11. B. Men must agree to use barrier contraception (ie, condoms) except when infertility is documented (eg, bilateral orchidectomy or azospermia and/or infertility secondary to CF)
12. $FEV_1 \geq 70\%$ of predicted normal for age, gender, and height (post-bronchodilator value using NHANES III standards) at screening
13. Stable lung function determined by the treating physicia, provided FEV_1 at Day -1 is within 10% of FEV_1 at screening.

NOTE: Eligibility criteria 14 through 20 relate to acceptable laboratory values at screening. Subjects with a screening laboratory value outside the specified range may be permitted if the value is not clinically significant in the opinion of the Investigator, with concurrence from the Sponsor's Medical Monitor.

14. Total WBC $\leq$ 12,000/μL
15. Hemoglobin > 10 g/dL
16. Hematocrit > 30%
17. Platelet count between 150 and 450 x 10^3/μL
18. Prothrombin time, international normalized ratio (INR) and partial thromboplastin time within normal limits
19. Serum albumin > 2.5 g/dL at screening
20. Liver function tests within 2X the upper limit of normal (SGPT/ALT, SGOT/AST, GGT, alkaline phosphatase, bilirubin [total and direct])

5.4 Exclusion Criteria

1. Personal or family history of prolonged QT syndrome; or a QTc interval > 430 msec (males) or > 450 msec (females) using Bazett's formula (QTcB)
2. Change in body weight within 90 days prior to Day 1 that is considered clinically significant by the Investigator
3. Abnormal vital signs at screening: heart rate > 120 bpm at rest; systolic blood pressure > 140 or < 90 mmHg; respiration rate > 24 bpm; and SpO2 < 92% at rest
4. History of alcohol abuse within the past 24 months or positive drug test at screening. Presence of drug(s) administered for known conditions are permitted with concurrence from the Sponsor's Medical Monitor (eg, benzodiazepine, oral cannabis).
5. Any infection including acute upper respiratory or lower respiratory infections, pulmonary exacerbation, changes in therapy for pulmonary disease, or any non

CF-related illness which results in the initiation of any new therapy within 30 days prior to Day 1

6. Clinically significant, abnormal screening laboratory value (as determined by the Investigator) or any abnormal screening laboratory value that would place the subject at undue risk while participating in the study (as determined by the Investigator with concurrence from the Sponsor's Medical Monitor)
7. Breast-feeding or pregnant female
8. Significant change in maintenance medications for CF within 30 days of Day 1
9. Use of lumacaftor or ivacaftor within 45 days of Day 1
10. Use of any investigational drug (other than QR-010) or device within 30 days of Day 1
11. Unable to or unwilling to perform key safety evaluations such as spirometry
12. Unable to participate in standardized airway clearance techniques
13. Presence or medical history of clinically significant disease which precludes study participation or prevents determination of outcome measures
14. History of lung transplantation
15. Hemoptysis of greater than 30 mLs within 90 days prior to Day 1, or hospitalization for hemoptysis within 6 months of Day 1
16. Any severe, acute, or chronic medical or psychiatric condition, laboratory abnormality, or other condition that, in the judgment of the Investigator, would place the subject at undue risk, interfere with the results of the study or make the subject otherwise unsuitable
17. Any difficulty complying with protocol requirements that may increase the risk associated with study participation or study drug administration or may interfere with safety

5.5 Study Completion and Discontinuation Criteria

5.5.1 Study Completion/Withdrawal

A subject will have the right to withdraw from the study at any time for any reason.

A subject will be discontinued from the study by the Investigator if unacceptable toxicity or withdrawal of consent occurs.

Subjects participating in a MAD cohort that is determined to be greater than the MTD based on dose escalation rules can opt to continue in the study at the next lower dose cohort (ie, at the MTD).

Subjects withdrawn from SAD cohorts should have all assessments conducted at the End of Study Visit at the time of withdrawal. Subjects withdrawn from MAD cohorts should have all

assessments conducted at the End of Treatment Visit as well as the End of Study Visit, for safety monitoring purposes.

Subjects who have completed a SAD cohort are eligible to participate in a MAD cohort, provided there is at least 90 days between the dose in the SAD cohort and the first dose in the MAD cohort.

Allergic reactions may include local dermatitis, angioedema, throat constriction, or anaphylaxis. Appropriate treatment may include administration of antihistamines, hydrocortisone, or epinephrine at the discretion of the assessing physician. Subjects diagnosed with a systemic allergic reaction requiring therapy will be withdrawn from the study.

Given the proposed mechanism of action of QR-010, it could be anticipated that subjects could experience a change in baseline cough, change in sputum quality, or change in sputum volume. A pulmonary exacerbation should be considered if these symptoms are accompanied by fever, body weight loss, generalized malaise. If a pulmonary exacerbation is diagnosed, appropriate interventions including appropriate additional antibiotics should be prescribed by the Investigator or treating physician. Subjects diagnosed with a pulmonary exacerbation requiring the addition of antibiotics will be withdrawn from the study.

5.5.2 Criteria for Study Drug Discontinuation

Subjects should be continued on study treatment unless an intolerable AE is experienced, or until an SAE and/or Grade ≥ 2 AE in the same system organ class is experienced by two or more subjects in the same cohort. Study treatment for that dose cohort should be stopped and subjects advised regarding available treatment options.

When study treatment is discontinued in the MAD cohorts due to an intolerable AE, the Investigator should obtain all procedures specified for the End of Treatment Visit, followed by an End of Study Visit, conducted 28 days after the last study drug dose.

5.5.3 Stopping Rules

5.5.3.1 Stopping Rules for Study

The DSMC will evaluate the safety data after each dose cohort and thereafter on an ongoing basis to recommend if the study should continue or cease, or if any modifications should be made as to how subjects are treated or managed.

5.5.3.2 Stopping Rules for Individual Subjects

For individual subjects in the SAD cohorts, any of the criteria below will result in discontinuation of study drug administration in the SAD portion of the study, as well as exclusion from participation in the MAD portion. These subjects will continue to be followed for safety through the End of Study visit.

- Any SAE suspected of being related to study drug
- Any Grade ≥ 2 AE suspected of being related to study drug
- Decrease in absolute FEV_1 volume of ≥ 15% from baseline value following study drug administration
- Unacceptable toxicity considered by the Investigator to be related to study drug treatment
- Further treatment is deemed to be unsafe in the Investigator's clinical judgment. The decision to discontinue a subject may also result from any clinically significant alteration in any clinical or laboratory finding
- If at any time the subject fails to follow the requirements of the protocol
- The subject withdraws consent. Subjects may withdraw from the study at any time without repercussion to their treatment or affiliation with their healthcare providers.

For individual subjects in the MAD cohorts, any of the following will result in permanent discontinuation of study drug:

- Any SAE suspected of being related to study drug
- Any Grade ≥2 AE suspected of being related to study drug
- Cumulative decrease in absolute FEV_1 volume of ≥ 15% from baseline value following study drug administration
- Unacceptable toxicity considered by the Investigator to be related to study drug treatment
- Further treatment is deemed to be unsafe in the Investigator's clinical judgment. The decision to discontinue a subject may also result from any clinically significant alteration in any clinical or laboratory finding
- If at any time the subject fails to follow the requirements of the protocol
- The subject withdraws consent. Subjects may withdraw from the study at any time without repercussion to their treatment or affiliation with their healthcare providers.

If study drug is discontinued for any of these stopping rules, administration will not be resumed, even after resolution of the event.

6.0 INVESTIGATIONAL PRODUCT(S)/STUDY MEDICATIONS

6.1 Investigational Product

6.1.1 QR-010

The investigational drug product, QR-010 Solution for Nebulization, is available at a concentration of 50 mg/mL (2 mL/vial) in a sterile isotonic solution of sodium chloride in water for injection. QR-010 Solution for Nebulization is a clear, colorless solution. The pH is between 6 and 8, and QR-010 Solution for Nebulization storage condition is 2-8°C. QR-010 Solution for

Nebulization will be administered to the subjects via oral inhalation, using the designated nebulizer.

6.1.2 Diluent and Placebo

Placebo Solution for Nebulization will be the same as the diluent for QR-010 Solution for Nebulization. It is 10 mL 0.9% isotonic solution of sodium chloride in water for injection. It is a clear, colorless solution. Placebo Solution for Nebulization will be administered to the subjects via inhalation, using the nebulizer described in Section 6.2.

6.1.3 Packaging and Labeling

QR-010 Solution for Nebulization is supplied in 2 mL Type 1 glass vials with a grey bromobutyl rubber stopper and a light blue tear off seal. Vials are packed into an outer carton, which is labeled per country-specific requirements.

Placebo Solution for Nebulization is packaged in 10 mL individual, sterile plastic vial/ampules.

Each vial/ampule and carton is labelled to comply with local guidelines.

6.1.4 Drug Shipment and Storage

An initial supply of QR-010 Solution for Nebulization will be shipped refrigerated (2-8°C) to the site investigational pharmacy upon completion of site activation process. Re-supply will occur through the central inventory management system. The drug should be stored refrigerated in the site pharmacy or a designated locked area at 2-8°C until use.

Please refer to the Study Manual for additional details on site activation, drug supply and the central inventory management system.

6.1.5 Drug Accountability and Reconciliation

The Investigator must designate a research pharmacist or other staff member to be unblinded and maintain an inventory record of drugs received and dispensed. Used vials should be retained for drug accountability by the site monitor, unless prohibited by local procedures, in which case an alternative drug accountability process will be agreed upon with the Sponsor. It is acceptable to destroy used vials per site standard operating procedure (SOP) after drug accountability has been completed by the site monitor. Additional details on study drug handling will be provided in the Pharmacy Manual.

Forms will be provided to facilitate the inventory control. These forms must be used unless the Investigator has previously established a system that complies with local regulations and is approved by Sponsor. The study drug must be dispensed only at the institution(s) specified on form FDA 1572 or Statement of Investigator (as applicable).

Upon completion or termination of the study and after inventory by a Sponsor-designated monitor, it will be determined if unopened drug is to be sent to the Sponsor in the original containers or is to be destroyed on site. Residual solutions must be discarded after use.

6.1.6 Dosage and Administration

The pharmacist (or other personnel qualified to prepare study drug for administration) at each site will receive study drug and will prepare and/or dilute the study drug according to the Pharmacy Manual for each administration. Pharmacy staff will be unblinded to subject treatment assignment (as assigned by the designated randomization system for the study). All other study site staff, including the Investigator and subjects, will be blinded to study treatment assignment.

Study drug doses will only be administered by a healthcare professional in an in-clinic setting. No at-home dose administration will be allowed. Subjects will receive study drug by inhalation via nebulizer. No other medications should be mixed with study drug in the nebulizer medication chamber. Appropriate study drug dilutions or placebo will be prepared by an Unblinded Study Pharmacist, as detailed in the Pharmacy Manual. The prepared doses will be loaded into the nebulizer medication chamber by study staff just prior to administration to the subject.

6.1.7 Overdose

The effects of overdose of this product are not known.

6.1.8 Premedication

For subjects whose standard CF medications include a short-acting β-agonist (SABA), the SABA should be administered within 15 minutes to 2 hours prior to the first study drug dose. If no adverse reaction occurs with the first dose, subsequent doses need not be preceeded by a SABA, as determined by the Investigator.

For those subjects whose standard CF medications include a long-acting β-agonist (LABA), the LABA should be administered between 1 and 4 hours prior to each study drug dose.

6.2 Nebulizer

6.2.1 eFlow Nebulizer System

The eFlow® Nebulizer System [redacted] will be used for study drug administration in the EU. The Investigational eFlow® Nebulizer System [redacted] will be used for study drug administration in North America.

Study drug dose dilutions prepared by the unblinded pharmacist will be provided to the study staff (who are blinded to the treatment assignment) who will load the medication chamber of the eFlow nebulizer with the study drug dose specified by randomization. The nebulizer Instructions for Use will be followed for all subjects for study drug administration. To minimize cross contamination between subjects, a new nebulizer handset will be provided for each dose.

Study drug will be administered in the clinic by qualified site personnel via the designated study nebulizer, until all study drug solution has been administered. Complete administration of study drug/placebo, if uninterrupted, should take approximately less than 20 minutes (a minimal amount of study drug solution will remain in the nebulizer medication chamber—this is normal).

6.3 Concomitant Medications and Ancillary Therapy

6.3.1 Permitted Concomitant Medications

All concurrent CF therapies should be continued for the duration of the study. Prior to study drug dosing on a given day, the following order of concurrent treatment should be adhered to: Long- and/or Short acting bronchodilator, mucolytic therapy (eg, Pulmozyme), chest physiotherapy (airway clearance technique), inhaled corticosteroid, inhaled antibiotics.

Subjects who are prescribed chronic, intermittent inhaled antibiotics should participate in the study when they are most stable and continue the inhaled antibiotic throughout the study. For most patients, this would mean that the subject initiates the inhaled antibiotic during the screening period and continues taking it as prescribed through the end of study, including some additional days or weeks. As the regimens of chronic inhaled antibiotics varies significantly from patients to patient, the Investigator is encouraged to discuss with the Sponsor's Medical Monitor the appropriate regimen for the course of the study.

Ancillary therapy regimens and airway clearance techniques should remain consistent throughout the study period. Other ancillary therapy may be administered at the discretion of the Investigator. Subjects should receive full supportive care, including antibiotics, antiemetics, bronchodilators, etc., as appropriate. The reason(s) for ancillary therapy, including dosage and date(s) of treatment, will be recorded in the source documents.

6.3.2 Prohibited Concomitant Medications

Oral corticosteroid medications may not be used prophylactically with the first dose. Chronic administration of oral corticosteroids at a stable dosage for at least 30 days prior to enrollment are permitted. The reason(s) for ancillary therapy, including dosage and date(s) of treatment, will be recorded in the source documents. Use of ivacaftor (Kalydeco™) or lumacaftor are prohibited within 45 days of Day 1, through the End of Study visit. Use of any investigational drug (other than QR-010) or device are prohibited within 30 days of Day 1, through the End of Study visit. If the subject received therapy with ivacaftor or lumacaftor within 90 days prior to Day 1, the start and stop dates will be recorded in the source documents and CRF.

6.3.3 Adequate Forms of Birth Control

Women of child bearing potential must agree to use a highly effective method of birth control from the list below (defined as those, alone or in combination, that result in a low failure rate, ie, less than 1% per year when used consistently and correctly). Double barrier methods (a combination of condom with cap, diaphragm, or sponge with spermicide) are not considered

highly effective. Childbearing potential is defined as being fertile following menarche and until becoming post-menopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Highly effective methods of birth control include:

- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner (provided that partner is the sole sexual partner and has received medical assessment of the surgical success)
- Sexual abstinence. Sexual abstinence must be true abstinence which is the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the trial, and withdrawal are not acceptable methods of contraception.

Birth control measures must be employed during the time of participation (beginning at the Screening Visit) in this trial. Protections against pregnancy must be continued for at least 3 months after the last dose of study drug.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. Male subjects with CF with medical confirmation of azospermia and/or infertility will be considered permanently sterile. A man who is fertile should use a condom during treatment and until 90 days after the last dose of study drug.

6.4 Adverse Reaction Management

AEs in the study will be treated with appropriate therapies. Acute bronchospasm (defined as a ≥ 15 % decrease in FEV_1 % predicted) should be treated with treatment cessation and with β2 agonists, IV hydrocortisone (100 mg), or other agents as appropriate. Additional supportive care should be provided as necessary by qualified staff with emergency resuscitation equipment.

A Grade 4 (as defined by Common Terminology Criteria for Adverse Events [NCI CTCAE Version 4.03] Modified for CF) adverse reaction requires permanent discontinuation of study drug.

If Grade 2-3 toxicity is noted during the dose administration, the administration should be halted and the subject assessed. If the adverse reaction symptoms resolve promptly, then study drug

administration may be re-initiated. Any Grade ≥ 2 adverse reaction suspected of being related to study drug will result in study drug discontinuation.

7.0 EVALUATIONS BY VISIT

All tests and procedures are detailed in Appendix 1, Schedule of Assessments. All laboratory tests are detailed in Appendix 2, Schedule of Laboratory Assessments. Refer to these appendices for the required assessments for each study day. Throughout the protocol, the term "baseline" is used to refer to tests or procedures performed at screening, Day -1, or on Day 1 prior to dosing.

7.1 Visit and Assessment Windows

The flexibility regarding scheduling of study days and corresponding procedures differ depending on the cohort and phase of the study. The timing of assessments, procedures and sample collections outlined in the protocol are nominal times. It is understood that in the phase 1 setting, actual times will approximate rather than match the nominal times exactly. Actual times are to be recorded in the source documentation and in the case report forms (CRFs), and, if any time points are missed, the reasons are also recorded.

For the SAD cohorts, there is no flexibility regarding the timing of the scheduled study days in relation to dose Day 1.

For the MAD cohorts, there is some flexibility regarding the timing of the scheduled study days in relation to dose Day 1. The description of procedures assumes a Monday-Wednesday-Friday dosing schedule. An alternative dosing schedule can be used, provided that there is at a minimum 2 days between doses, and a maximum of 4 days between doses. Missed doses are to be recorded as such, and the overall treatment period should remain at 4 weeks, and not be extended to accommodate the missed doses. Missed doses are to be recorded in the CRF.

Details regarding acceptable windows for timing of study procedures for both the SAD and MAD cohorts can be found in the Laboratory Manual.

7.2 Screening Visit (All Cohorts)

A screening log of all consented subjects will be kept at each site. Subject screening should be conducted ≤ 14 days prior to study drug dosing (Day 1). Screening evaluations may be completed over several days, if necessary.

If the first administration of study drug does not occur within the initial 14 days of screening, the screening period may be extended up to an additional 14 days and subjects may be reassessed for eligibility with an interim medical history, focused physical examination, and repeat of laboratory studies (standard laboratory assessments).

At the discretion of the Sponsor's Medical Monitor, the screening period for an individual subject may be extended for an additional 7 days. In this case, the subject may be reassessed for

eligibility with an interim medical history and repetition of all screening assessments, with the exception of sweat chloride, 12-lead ECG, chest Xray and CFTR genotyping.

If the screening period extends beyond 28 days (or up to 35 days with concurrence of the Sponsor's Medical Monitor), the potential subject will be considered a screening failure, but may be re-screened at a later date.

All screening evaluations must be reviewed by the Investigator to establish subject eligibility before dosing the subject for this study. Local laboratory results will determine subject eligibility for laboratory criteria.

The following screening evaluations should be obtained for all subjects:

1. Informed consent
2. Review of inclusion/exclusion criteria (Selection of Subjects)
3. Review of medical history
4. Demographics
5. Complete physical examination (including height and body weight)
6. Vital signs: blood pressure, heart rate, respiratory rate, and temperature
7. Oximetry
8. Chest Xray
9. Review of concomitant medication (record all medication within 30 days prior to screening), including prescription medications, over the counter (OTC) medications, herbal preparations, and use of lumacaftor or ivacaftor within 90 days prior to Day 1
10. Twelve-lead ECG
11. Spirometry (FEV_1, FVC, and FEF_{25-75})
12. Obtain urine sample for local laboratory assessments
13. Obtain urine or blood sample for drug screen
14. Obtain urine or blood sample for pregnancy test (for women of child-bearing potential)
15. Obtain blood samples for local laboratory assessments
16. Obtain blood and sputum for inflammatory biomarkers
17. Obtain blood sample for CFTR genotyping (if adequate prior documentation is not available)
18. Obtain sample for sweat chloride determination

7.3 SAD Cohorts (Cohorts 1-4)

7.3.1 Day -1 (Start of In-Clinic Phase)

1. Confirm study eligibility
2. Complete physical examination (including body weight)
3. Vital signs: blood pressure, heart rate, respiratory rate, and temperature measured
4. Oximetry
5. Concomitant medication review
6. AE review
7. Obtain blood and urine samples for local laboratory assessments (only assessments that were abnormal but not clinically significant at screening)
8. Obtain urine or blood sample for pregnancy test (for women of child-bearing potential)
9. Obtain sputum sample for the following local laboratory assessment:
   - Microbiology organism identification
10. Obtain blood sample for CFTR sequencing (required, separate consent form may be required). Note: this blood sample may be collected on Day 1 pre-dose instead of Day -1.
11. Obtain blood and sputum samples for inflammatory biomarkers. Note: these blood and sputum samples may be collected on Day 1 pre-dose instead of Day -1.
12. Spirometry (FEV_1, FVC, and FEF_{25-75}) post administration of short-acting bronchodilator

7.3.2 Day 1

Pre-dose:

1. Symptom-directed physical examination (including body weight)
2. Vital signs
3. Oximetry
4. Concomitant medications review
5. AE review
6. Administer any routine pulmonary medications and airway clearance techniques, including SABA and/or LABA, Pulmozyme, inhaled corticosteroids and/or antibiotics
7. Initiate continuous cardiac and vital signs monitoring and continue for 24 hours post dose
8. Spirometry (FEV_1, FVC, and FEF_{25-75})
9. Obtain blood samples for local laboratory assessments
10. Obtain urine sample for urinalysis (Time 0, pre-dose)

11. Obtain blood and urine samples for PK (Time 0, pre-dose)

Study Drug Administration:

Study drug to be administered by qualified site personnel via the designated study nebulizer, until all study drug solution has been administered. Subjects are to be seated during the entire duration of study drug administration, inhaling the nebulized study drug using normal tidal breathing (no noseclips). Details regarding study drug preparation, device preparation and handling, as well as administration of study drug will be included in the Pharmacy Manual and Study Manual.

Post-dose:

1. Symptom-directed physical examination at 15, 60 minutes, 2, 3, 4, 6, 8, and 12 hours post dose
2. Vital signs at 1, 10, 30, 60 minutes, 2, 4, 12 hours post dose
3. Oximetry at 1, 10, 30, 60 minutes, 2, 4, 12 hours post dose
4. Concomitant medications review
5. AE review
6. Spirometry at 10, 30, and 60 minutes, and 2, 4, and 8 hours post dose
7. Obtain blood samples for local laboratory assessments at 30, 60 minutes, 2, 4, 8, and 12 hours post dose
   - Complete blood count (CBC) with absolute differential
   - Serum chemistry
8. Obtain the following samples for PK:
   - Blood at 0.5, 1, 2, 3, 4, 12 hours post dose
   - Pooled urine from 0 to 4 hours, 4 to 12 hours, and 12 to 24 hours post dose. Subjects should empty their bladders just prior to dosing and at the end of each time interval for the final urine collection of that interval. Urinalysis by dipstick will be performed on the pooled urine samples for each time interval.
   - Sputum at 3 times post dose, within the first 6 hours post dose. Suggest obtaining samples in conjunction with performing spirometry at 10, 60 minutes, and 4 hours post dose.

7.3.3 Day 2

1. Symptom-directed physical examination
2. Vital signs
3. Oximetry

4. Review of concomitant medications
5. AE review
6. Spirometry
7. Obtain blood and urine samples for local laboratory assessments 24 hours post dose
8. Obtain the following samples for PK:
   - Blood at 24 hours post dose
   - Urine at 24 hours post dose
   - Sputum at 24 hours post dose
9. Obtain blood and sputum samples for inflammatory biomarkers (24 hours post dose)

7.3.4 Day 3

1. Vital signs
2. Oximetry
3. Concomitant medications review
4. AE review
5. Obtain blood and urine samples for local laboratory assessments 48 hours post dose
6. Obtain the following samples for PK:
   - Blood at 48 hours post dose
   - Urine at 48 hours post dose

7.3.5 Day 4 (Day of Discharge)

1. Symptom-directed physical examination
2. Vital signs
3. Oximetry
4. Review of concomitant medications
5. AE review
6. Spirometry
7. Obtain blood and urine samples for local laboratory assessments
8. Obtain blood and sputum samples for inflammatory biomarkers
9. Obtain the following samples for PK:
   - Blood at 54 and 72 hours post dose
   - Urine at 72 hours post dose

- Sputum at any time prior to discharge

10. Discharge subject

7.3.6 Day 8 End of Study Visit

If at any time during the study the subject discontinues the study early, the subject should return to the clinic to complete the End of Study Visit procedures below.

1. Complete physical examination (including body weight)
2. Vital signs
3. Oximetry
4. Concomitant medications review
5. AE review
6. Chest Xray for subjects who experience pulmonary AEs during the study
7. 12-lead ECG
8. Spirometry
9. Obtain blood and urine samples for local laboratory assessments
10. Obtain urine or blood sample for pregnancy test (for women of child-bearing potential)
11. Obtain blood, urine, and sputum samples for PK 168 hours post dose. Sputum for PK may be obtained at any time during the visit.
12. Obtain sputum sample for the following local laboratory assessment:
    - Microbiology organism identification
13. Obtain blood and sputum samples for inflammatory biomarkers

7.4 MAD Cohorts (Cohorts 5-8)

7.4.1 Dosing Schedule

Study drug will be administered in the clinic for all dosing days. The dosing schedule below assumes a Monday-Wednesday-Friday (thrice-weekly or tiw) dosing scheme. Subjects will be observed until 12 hours post dose on Day 1 and Day 3. The subject will return to the clinic for all subsequent doses and required assessments.

7.4.2 Day -1

1. Confirm study eligibility
2. Complete physical examination (including body weight)
3. Vital signs: blood pressure, heart rate, respiratory rate, and temperature measured
4. Oximetry

5. Concomitant medication review
6. AE review
7. Obtain blood and urine for local laboratory assessments (only assessments that were abnormal but not clinically significant at screening)
8. Obtain urine or blood for pregnancy test (for women of child-bearing potential)
9. Obtain sputum sample for the following local laboratory assessment:
   - Microbiology organism identification
10. Obtain blood samples for CFTR sequencing (required, separate consent form may be required). Note: this blood sample may be collected on Day 1 pre-dose instead of Day -1, and should not be collected if subject already participated in a SAD cohort.
11. Obtain blood and sputum samples for inflammatory biomarkers. Note: these blood and sputum samples may be collected on Day 1 pre-dose instead of Day -1.
12. Spirometry (FEV_1, FVC, and FEF_{25-75}) post administration of short-acting bronchodilator

7.4.3 Week 1, Day 1 (Dose 1)

Pre-dose:

1. Subject self-completes the CFQ-R prior to all other procedures and assessments
2. Symptom directed physical examination (including body weight)
3. Vital signs
4. Oximetry
5. Concomitant medications review
6. AE review
7. Administer any routine pulmonary medications and airway clearance techniques, including SABA and/or LABA, Pulmozyme, inhaled corticosteroids and/or antibiotics
8. Initiate continuous cardiac and vital signs monitoring and continue for 12 hours post dose
9. Spirometry (FEV_1, FVC, and FEF_{25-75}), post administration of short-acting bronchodilator
10. Obtain blood samples for local laboratory assessments
11. Obtain urine sample for urinalysis (Time 0/pre-dose)
12. Obtain blood and urine samples for PK (Time 0/pre-dose)

Study Drug Administration:

Study drug to be administered by qualified site personnel via the designated study nebulizer, until all study drug solution has been administered. Subjects are to be seated during the entire

duration of study drug administration, inhaling the nebulized study drug using normal tidal breathing (no noseclips). Details regarding study drug preparation, device preparation and handling, as well as administration of study drug will be included in the Pharmacy Manual and Study Manual.

Post-dose:

1. Symptom-directed physical examination at 15, 60 minutes, 2, 4, 6, 8, and 12 hours post dose
2. Vital signs at 1, 10, 30, 60 minutes, 2, 4, and 12 hours post dose
3. Oximetry at 1, 10, 30, 60 minutes, 2, 4, and 12 hours post dose
4. Concomitant medications review
5. AE review
6. Spirometry at 10, 30, and 60 minutes, and 2, 4, and 8 hours post dose
7. Obtain blood samples for local laboratory assessments at 30, 60 minutes, 2, 4, 8, and 12 hours post dose
   - Complete blood count (CBC) with absolute differential
   - Serum chemistry
8. Obtain the following samples for PK:
   - Blood at 0.5, 1, 2, 3, 4, 12 hours post dose
   - Pooled urine from 0 to 4 hours and 4 to 12 hours post dose. Subjects should empty their bladders just prior to dosing and at the end of each time interval for the final urine collection of that interval. Urinalysis by dipstick will be performed on the pooled urine samples for each time interval.
   - Sputum at 3 times post dose, within the first 6 hours post dose. Suggest obtaining samples in conjunction with performing spirometry at 10, 60 minutes, and 4 hours post dose.
9. Discharge subject

7.4.4 Week 1, Day 3 (Dose 2)

Pre-dose:

1. Symptom-directed physical examination
2. Vital signs
3. Oximetry
4. Concomitant medications review
5. AE review

6. Administer any routine pulmonary medications and airway clearance techniques, including SABA and/or LABA, Pulmozyme, inhaled corticosteroids and/or antibiotics
7. Obtain blood for PK sample prior to dosing (approximately 48 hours post dose 1)
8. Administer study drug

Post-dose:

1. Symptom-directed physical examination at 15, 60 minutes, 4, 8, and 12 hours post dose
2. Vital signs at 1, 10, 30, 60 minutes, 2, 4 and 12 hours post dose
3. Oximetry at 1, 10, 30, 60 minutes, 2, 4 and 12 hours post dose
4. AE review
5. Spirometry at 20, and 60 minutes, and 4 hours post dose
6. Obtain blood samples for local laboratory assessments at 60 minutes and 4 hours post dose
   - Complete blood count (CBC) with absolute differential
   - Serum chemistry
7. Obtain urine sample for local urinalysis at 60 minutes and 4 hours post dose
8. Obtain blood sample for PK at 2 hours post dose
9. Discharge subject

7.4.5 Week 1, Day 4

1. Symptom-directed physical examination
2. Vital signs
3. Oximetry
4. Concomitant medications review
5. AE review
6. Spirometry
7. Obtain blood and urine samples for local laboratory assessments
8. Obtain blood and sputum samples for inflammatory biomarkers
9. Obtain the following samples for PK (approximately 72 hours post dose 1):
   - Blood, urine, and sputum

7.4.6 Week 1, Day 5 (Dose 3)

Pre-dose:

1. Symptom-directed physical examination
2. Vital signs
3. Oximetry
4. Concomitant medications review
5. AE review
6. Administer any routine pulmonary medications and airway clearance techniques, including SABA and/or LABA, Pulmozyme, inhaled corticosteroids and/or antibiotics
7. Spirometry (FEV_1, FVC, and FEF_{25-75})
8. Obtain blood sample for PK (approximately 96 hours post dose 1)
9. Administer study drug

Post-dose:

1. Symptom-directed physical examination at 15, 60 minutes, and 2 hours post dose
2. Vital signs at 1, 10, 30, 60 minutes, and 2 hours post dose
3. Oximetry at 1, 10, 30, 60 minutes, and 2 hours post dose
4. AE review
5. Spirometry at 20, and 60 minutes, and 4 hours post dose (if FEV_1 at 60 minutes was decreased 15% from pre-dose value)

7.4.7 Weeks 2, 3 and 4 (Doses 4, 7, and 10)

Pre-dose

1. Subject self-completes the CFQ-R prior to all other procedures and assessments (Week 3 dose 7 only)
2. Complete physical examination (including body weight)
3. Vital signs
4. Oximetry
5. Concomitant medications review
6. AE review
7. Administer any routine pulmonary medications and airway clearance techniques, including SABA and/or LABA, Pulmozyme, inhaled corticosteroids and/or antibiotics

8. Spirometry (FEV_1, FVC, and FEF_{25-75})
9. Obtain blood and urine samples for local laboratory assessments
10. Obtain blood sample for PK
11. Obtain pre-dose sputum sample for PK (prior to dose 4 only). Suggest obtaining sample in conjunction with performing spirometry prior to dosing
12. Obtain blood and sputum samples for inflammatory biomarkers
13. Administer study drug

Post-dose:

1. Symptom-directed physical examination at 15, 60 minutes, 2 hours post dose
2. Vital signs at 1, 10, 30, 60 minutes, 2 hours post dose
3. Oximetry at 1, 10, 30, 60 minutes, 2 hours post dose
4. Concomitant medications review
5. AE review
6. Spirometry at 20, and 60 minutes post dose
7. Obtain blood samples for local laboratory assessments at 15, 60 minutes, 2 hours post dose
8. Obtain blood for PK at 1 hour post dose 7 only
9. Obtain urine sample for urinalysis at 60 minutes and 2 hours post dose

7.4.8 Weeks 2, 3, and 4 (Doses 5, 6, 8, 9 and 11)

1. Symptom-directed physical examination
2. Vital signs
3. Oximetry
4. Concomitant medications review
5. AE review
6. Confirm administration of all routine pulmonary medications and airway clearance techniques prior to administration of study drug
7. Obtain blood for PK prior to dosing
8. Obtain pre-dose sputum for PK (prior to doses 5 and 6 only)
9. Administer study drug

7.4.9 Week 4 (Dose 12)

Pre-dose:

1. Complete physical examination (including body weight)
2. Vital signs
3. Oximetry
4. Concomitant medications review
5. AE review
6. Obtain blood and urine samples for PK prior to dosing
7. Administer any routine pulmonary medications and airway clearance techniques, including SABA and/or LABA, Pulmozyme, inhaled corticosteroids and/or antibiotics
8. Spirometry (FEV_1, FVC, and FEF_{25-75})
9. Administer study drug

Post-dose:

1. Symptom-directed physical examination within 2 hours post dose
2. Vital signs within 2 hours post dose
3. Oximetry within 2 hours post dose
4. Spirometry at 20, and 60 minutes, 4 hours post dose
5. Obtain the following samples for PK:
   - Blood at 1, 2, 3, 4, and 8 hours post dose
6. Obtain sample for sweat chloride determination

7.4.10 Follow-up Visit for PK—24 hours +/- 12 hours After Last Dose

Subject to return to clinic to obtain serum and urine samples for PK. The samples can be collected any time within the time window specified.

7.4.11 Follow-up Visit for PK—96 hours +/- 48 hours After Last Dose

Subject to return to clinic to obtain serum and urine samples for PK. The samples can be collected any time within the time window specified.

7.4.12 Follow-up Visits—7 and 28 Days After Last Dose

Follow-up visits will occur 7 and 28 days after the last dose of study drug (dose 12).

If at any time during the study the subject discontinues the study early, the subject should return to the clinic to complete the End of Treatment Visit procedures below, and should also return to the clinic to complete the End of Study Visit procedures 28 days after the last study drug dose.

7.4.12.1 7 Days After Last Dose—End of Treatment Visit

1. Subject self-completes the CFQ-R prior to all other procedures and assessments
2. Complete physical examination (including body weight)
3. Vital signs
4. Oximetry
5. Concomitant medication review
6. AE review
7. Chest Xray
8. 12-lead ECG
9. Spirometry
10. Obtain blood and urine samples for local laboratory assessments
11. Obtain urine or blood for pregnancy test (for women of child-bearing potential)
12. Obtain blood samples for PK
13. Obtain sputum sample for the following local laboratory assessment:
    - Microbiology organism identification
14. Obtain blood and sputum samples for inflammatory biomarkers
15. Obtain sample for sweat chloride determination

7.4.12.2 28 Days After Last Dose—End of Study Visit

1. Subject self-completes the CFQ-R prior to all other procedures and assessments
2. Complete physical examination (including body weight)
3. Vital signs
4. Oximetry
5. Concomitant medication review
6. AE review
7. Spirometry
8. Obtain blood and urine samples for local laboratory assessments
9. Obtain urine or blood for pregnancy test (for women of child-bearing potential)
10. Obtain blood and sputum samples for inflammatory biomarkers

11. Obtain serum samples for PK

12. Obtain sample for sweat chloride determination

8.0 STUDY PROCEDURES

Safety parameters will be assessed by monitoring AEs, vital signs, oximetry, laboratory data (chemistries, hematology and urinalysis), ECGs, pulmonary function (spirometry), and physical examinations. AEs and SAEs including laboratory tests (chemistries, hematology, and urinalysis) and ECGs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Modified for CF (CTCAE v4.03).

8.1 Adverse Events

Information regarding occurrence of AEs will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relationship to study drug will be recorded. Refer to Section 12.0, Assessment of Safety or Adverse Events and Serious Adverse Events.

8.2 Vital Signs

Blood pressure, heart rate, respiration rate, and temperature will be measured at rest in a sitting position. During the first 24 hours post first dose (SAD cohorts) or 12 hours post first dose (MAD cohorts), vital signs will be monitored via Holter and automated vital signs monitoring.

8.3 Telemetry

On dosing Day 1, continuous cardiac and vital signs monitoring will be conducted. Recorded measurements (eg, via Holter monitoring) are acceptable (if observed monitoring is not available).

8.4 Oximetry

Digital oximetry will be measured at rest in a sitting position.

8.5 Laboratory Evaluations

Laboratory evaluations will be performed according to the study schedule. For screening purposes, should the screening period require longer than 14 days (eg, CFTR genotype testing required longer than 14 days), safety evaluations (serum chemistries, hematologies, urinalysis, physical exam, vital signs, spirometry) must be re-obtained for confirmation of eligibility and enrollment into the study.

Serum chemistries will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphorus, SGPT/ALT, SGOT/AST, GGT, alkaline phosphatase, bilirubin (total and direct), uric acid, lactic dehydrogenase (LDH), albumin,

total protein, triglycerides, and cholesterol. Creatinine clearance is to be calculated using the Cockcroft-Gault equation adjusted for actual body weight. At screening, tocopherol (Vitamin E) levels will also be measured.

Hematologies will include a complete blood count: Complete blood count (CBC) with absolute differential (hematocrit, hemoglobin, white blood count, segmented neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, platelet count).

A Direct Antiglobulin Test (DAT) will also be performed at screening and 7 days after last dose.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) will be measured at baseline, 24 hours post dose, and End of Study Visit for SAD cohorts, and at baseline, prior to doses 4, 7 and 10, and at the End of Treatment Visit for MAD cohorts. Two baseline measurements will be made; one on Day -1, and the other prior to dosing on Day 1.

Urinalysis (by visual inspection and dipstick) will include color and appearance, specific gravity, pH, protein, glucose, occult blood, ketones, bilirubin, leukocyte esterase, nitrite, and urobilinogen. In addition, microscopic analyses will be performed on samples with abnormal dipstick results. Urine microalbumin will be measured at baseline for SAD and MAD cohorts; end of study for SAD cohorts; and prior to dose 10 and end of study for MAD cohorts. Time of void will be recorded for each urine sample collected. At screening, testing for drugs of abuse will also be performed, specifically for amphetamines, methamphetamines, methylenedioixymethamphetamine, cocaine, cannabinoids, phencyclidine, opiates, methadone, barbiturates, benzodiapines, ethyl alcohol. Urine or blood testing for drugs of abuse is permitted.

Coagulation testing (INR, PT, PTT, fibrinogen) and total complement (CH50) will be performed at screening and the End of Study Visit for the SAD cohorts, and at screening, prior to dose 4, and at End of Treatment Visit for the MAD cohorts. Any abnormalities of coagulation will be followed with additional testing as determined by the Investigator and/or Medical Monitor to diagnose the coagulopathy.

For female subjects, a pregnancy test (preferably serum, but urine tests are also accepted) will also be obtained as designated by the study schedule.

Sputum for microbiology will be obtained as designated by the study schedule (for organism identification only).

8.6 Pharmacokinetic Evaluations

Samples for PK analysis will be collected as detailed in Appendix 1 and Appendix 2.

Expectorated sputum samples for PK assessment can be difficult to obtain at the specified time points. It is suggested that samples be collected in conjunction with spirometry, as often spirometry maneuvers can provoke coughing and sputum expectoration. Subjects should rinse their mouths with water or saline prior to collection of expectorated sputum samples.

Serum PK samples, when scheduled at time points when safety labs and/or biomarker samples are also to be collected, are to be collected first, followed by safety lab samples, and lastly biomarker samples.

Urine PK samples will be obtained over the following time intervals (in hours post dose administration completion): Pooled samples collected from 0 to 4 hours, 4 to 12 hours, and 12 to 24 hours post dose (SAD cohorts only), and at additional time points on subsequent study days (see Appendices 1 and 2 for specific timing of sample collection). Subjects should empty their bladders just prior to dosing and at the end of each time interval for the final urine collection of that interval. Urinalysis will be performed on each pooled sample prior to storage for PK analysis. Time and volume will be recorded for each void or urine collection interval at the designated time points.

8.7 Chest Xray

A chest radiograph should be obtained at screening for the SAD cohorts, and at end of study for subjects exhibiting pulmonary AEs. A chest radiograph or CT scan obtained within 90 days of Screening Visit is acceptable if there was no occurrence of intercurrent pulmonary illness during the interim.

A chest radiograph should be obtained at both screening and 7 days after last dose (end of treatment) for the MAD cohorts. A centralized reading of all chest radiographs may be performed at the end of the study.

8.8 Biomarkers

Immune response monitoring will be performed per Appendices 1 and 2. Biomarkers of interest will be measured in both blood and sputum, and may include cytokines and proteases. The immune profile seen may prompt further exploratory immune response biomarker analysis. Blood (serum and plasma) and expectorated sputum samples will be collected per the study schedule, and stored for later quantification.

8.9 Electrocardiogram (ECG)

12-lead ECG will be obtained at screening and end of study for the SAD cohorts, and at screening and 7 days post last dose for the MAD cohorts. 12-lead continuous telemetry will be obtained pre- and during the first 24 hours post first dose for SAD cohorts, and during the first 12 hours post first dose for MAD cohorts.

8.10 Pulmonary Function

Spirometry will be performed per American Thoracic Society (ATS)/European Respiratory Society (ERS) Standards. FEV_1, FVC, and FEF_{25-75} will be collected. Actual liter values will be recorded. Prior to study drug dosing on a given day, the following order of concurrent treatment should be adhered to: Long- and/or Short acting bronchodilator, mucolytic therapy (eg,

Pulmozyme), chest physiotherapy (airway clearance technique), inhaled corticosteroid, inhaled antibiotics. Ancillary therapy regimens and airway clearance techniques should remain consistent throughout the study period, and the order of therapies and medications should also remain the same.

8.11 Physical Examination

Complete physical examinations (urogenital exams not required) will be performed at screening, Day -1, prior to dosing for dose Days 4, 7, 10, and 12 (Cohorts 5-8), and at the End of Treatment and End of Study Visits. Symptom-directed physical exams will be performed at all other time points, as indicated by the study schedule.

8.12 Height and Weight

Height will be measured using a calibrated, wall-mounted stadiometer and will be documented at the Screening Visit. Body weight will be measured using a calibrated scale per study schedule.

8.13 Sweat Chloride

Documentation of pilocarpine iontophoresis sweat chloride of > 60 mmol/L is required for eligibility for all subjects. As sweat chloride is a measure of exploratory efficacy in the MAD cohorts, sweat chloride will be measured by pilocarpine iontopheresis at screening for all subjects, at the dose 12 Visit, and at the End of Treatment and End of Study follow-up visits for the MAD cohorts only. Determination of sweat chloride must be performed in an accredited laboratory using a method accepted by the Cystic Fibrosis Foundation and documented accordingly.

The sweat chloride sample collection at the dose 12 Visit can be performed pre- or post-dose.

8.14 CFQ-R

The CFQ-R subject health-related quality of life questionnaire will be administered using the self-administered format (Adult version) [Appendix 3], according to the study schedule for MAD cohorts only. The CFQ-R will be administered prior to any other test or procedure on each of the required study days.

8.15 CFTR Genotyping and Sequencing

Confirmation of CFTR gene mutations homozygous for the ΔF508 mutation are required for all subjects for eligibility. Genetic testing performed prior to the year 2000 must be re-confirmed, and a blood sample for CFTR genotyping should obtained at the Screening Visit. Genotyping results must be received and confirmed as homozygous for the ΔF508 mutation prior to randomization.

Complete CFTR gene sequencing will be performed for all subjects randomized into the study. Blood samples will be collected at baseline (Day -1 or Day 1 pre-dose), and stored until the end of the study for analysis.

Both CFTR genotyping and gene sequencing analysis are not optional for this study. Separate informed consent may be need to be obtained per local requirements.

9.0 OTHER CONSIDERATIONS

9.1 Routine CF Pulmonary Medications

Administer any routine pulmonary medications, including SABA and/or LABA, Pulmozyme, and inhaled corticosteroids and/or antibiotics, in the same order each dosing day, prior to spirometry and study drug dosing, during the in-house phase of the study.

9.2 Chest Physiotherapy

Any chest physiotherapy techniques utilized by an individual subject should remain consistent throughout the study. The order in which chest physiotherapy techniques are performed, in relation to other medications and administration of study drug should remain consistent throughout the study.

10.0 PHARMACOKINETIC AND EXPLORATORY EFFICACY MEASUREMENTS

10.1 Pharmacokinetic Measurements

Blood samples will be obtained from all subjects to obtain PK data pre- and post-dosing.

Samples for assessment of PK parameters of QR-010 ($C_{max,}$ $C_{min,}$ CL, V_d, AUC_{0-t} and $AUC_{0-\infty}$, and $t_{1/2}$) will be obtained only at the visits shown in Appendices 1 and 2.

10.2 Exploratory Efficacy Measurements

Exploratory efficacy response criteria will be evaluated per the schedule.

Efficacy Assessment 1

FEV_1

Efficacy Assessment 2

Sweat chloride measurement (MAD cohorts only)

Efficacy Assessment 3

CFQ-R Respiratory Symptoms Scale Score

Efficacy Assessment 4

Body weight

11.0 STUDY TERMINATION

If the Sponsor, DSMC, Sponsor's Medical Monitor or designee, study monitor, or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that a study center should be terminated, this action may be taken after appropriate consultation. Termination may occur in accordance with the clauses contained in the site's executed clinical trial agreement. ProQR Therapeutics reserves the right to discontinue the trial prior to enrollment of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons.

If the clinical development of QR-010 is discontinued, the Sponsor shall immediately inform all trial Investigators/institutions and regulatory authorities. Study termination and follow-up will be performed in compliance with the conditions set forth in the ICH E6 on Good Clinical Practice guidelines and local regulatory requirements.

12.0 ASSESSMENT OF SAFETY OR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All subjects who receive study drug will be assessed for safety.

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting the Sponsor regarding any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The Investigator is responsible for appropriate medical care of subjects during the study.

12.1 Data Safety Monitoring Committee

An independent DSMC from the Cystic Fibrosis Foundation Therapeutics Development Network Data and Safety Monitoring Board will provide safety oversight for the study. All DSMC members have significant experience with oversight of cystic fibrosis clinical trials. A DSMC operational charter will be finalized prior to randomization of the first subject. The DSMC will review unblinded safety data from each cohort, and provide their recommendation for proceeding to the next dosing cohort, as described in Section 4.2.

12.2 Definitions of Adverse Event

12.2.1 Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. AEs can include any unfavorable, noxious, unintended sign, symptom, or disease temporally associated with use of an investigational medicinal product or other protocol-imposed intervention, regardless of attribution. AEs may be spontaneously

reported by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory test, or other means.

AEs include:

- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period (as specified in Section 12.4.1)
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as blood draws)
- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (eg, invasive procedures such as blood draws, medication washout, or no treatment run-in)

12.3 Assessment of Adverse Events

The Investigator is responsible for assessing the severity and causality of AEs.

12.3.1 Assessment of the Severity (Intensity) of Adverse Events

Maximum intensity is to be graded using the NCI CTCAE (V 4.0) Modified for CF (National Cancer Institute, 2011). If grading table does not have grading criteria for the event, the criteria in Table 4 will be used.

Table 4: Adverse Event Intensity (Severity) Scale

Grade	Severity	Alternative Description of the Adverse Event[a]
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Minimal, local, or noninvasive intervention indicated; discomfort sufficient to reduce or interfere with daily activities.
3	Severe	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization may be indicated; disabling; limits self-care with significant interference with daily activities; incapacitating with inability to perform self care activities of daily living.
4	Life-threatening	Urgent intervention indicated; immediate risk of death.
5	Death	

Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions of an SAE.

a. Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI CTCAE Modified for CF listing.

Any AE that meets the seriousness criteria (see Section 12.5, Serious Adverse Event Definition) will be considered an SAE, including all life-threatening AEs. In addition, AEs with Grade 4 intensity may be considered serious if the event is determined to be clinically significant.

12.3.2 Assessment of the Relationship of Adverse Events to Study Drug

The Investigator will make a causality assessment about the relationship of each AE to study drug. Treatment-related conditions must be distinguished from disease-related conditions. To ensure consistency of AE and SAE causality assessments, Investigators should apply the following general guideline:

Not Related: The AE has an etiology other than the study drug (eg, preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the study drug (eg, cancer diagnosed 2 days after first dose of study drug).

Related: There is a plausible (possible, probable, or definite) temporal relationship between the onset of the AE and administration of the investigational product, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the investigational product; and/or the AE abates or resolves upon discontinuation of the investigational product or dose reduction and, if applicable, reappears upon rechallenge.

Note: The Investigator's assessment of causality for individual AE reports is part of the study documentation process and will be recorded in the subject's medical record, AE CRF, and SAE form if applicable. AEs recorded without the Investigator's assessment of the relationship to study drug will be followed up until causality is assigned.

12.3.3 Assessment of the Outcome of Adverse Events

Recovered/resolved: The subject has fully recovered from the event, with no residual effects observable.

Recovered/resolved with sequelae: The subject has recovered from the event, but with residual sequelae effects observable.

Not recovered/resolved: Effects of the event are still present.

Recovering/resolving: The subject has improved, but has not fully recovered from the event.

Fatal: The death is related to the event.

Unknown: The outcome of the event is unknown to the reporter (eg, subject was lost to follow-up).

12.4 Reporting of Adverse Events

The Investigator is responsible for ensuring that all AEs and SAEs are recorded in the source document, AE CRF, and/or SAE form, and reported to the Sponsor in accordance with protocol instructions.

12.4.1 Adverse Event Reporting Period

All significant medical conditions including signs/symptoms of the underlying diagnosis found during the screening period and up to randomization will be captured as medical history. Any event/condition related to participation in the trial but not related to underlying or concomitant disease that is noted after screening up to the randomization date will be captured as a non-treatment emergent AE.

Any event/condition noted once the subject is randomized will be captured as an AE. All AEs and SAEs regardless of attribution will be collected until at least 30 days following the last administration of study treatment or initiation of new therapy, whichever is earlier. At the last scheduled visit, the Investigator should instruct each subject to report to the Investigator any subsequent SAEs that the subject's personal physician believes could be related to prior study treatment. Any related non-serious AE occurring after the reporting period may be reported at the discretion of the Investigator.

AEs and SAEs related to study drug that persist >30 days after the last study drug dose should be followed until resolution or until they return to baseline, stabilize, the subject is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the AE CRF and SAE form (if applicable) and in the subject's medical record to facilitate source data verification. For some SAEs, the Sponsor or its designee may follow up by telephone, facsimile, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (eg, hospital discharge summary, consultant report, or autopsy report).

12.4.2 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

12.4.3 Recording Adverse and Serious Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the CRF and/or SAE form. Colloquialisms and abbreviations should be avoided. SAEs must also

be recorded on the AE CRF. Only one medical concept should be recorded in the event field on the AE CRF and SAE form (if applicable).

a. Signs and Symptoms versus Diagnosis

Signs and symptoms should be recorded on the AE CRF rather than the unifying diagnosis. The unifying event term or diagnosis should be recorded as the "etiology" in the CRF (if known), and the SAE form, if applicable. For example, jaundice, asterixis, and elevated transaminases should be recorded on the CRF, and "liver failure" should be recorded as the etiology. As another example, cough, rhinitis, and sneezing should be recorded as AEs on the CRF, and record "upper respiratory tract infection" as the etiology. Vague, nonspecific AE terms such as "erythema," "rash," or "lump on head" should be avoided and more specific information should be provided, such as "erythematous macule on right leg," "allergic dermatitis," and "scalp cyst."

b. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, cascade events or clinical sequelae) should also be entered as separate AEs. For example, if severe diarrhea is known to have resulted in dehydration, both diarrhea and dehydration should be entered as AEs on the CRF, and if also serious, on the SAE form.

c. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between subject evaluation time points. Such events should only be recorded once in the CRF unless their severity increases. If a persistent AE becomes more severe or occurs more frequently, it should be recorded again on the AE CRF with the increased severity grading.

A recurrent AE is one that occurs and resolves between subject evaluation time points and subsequently recurs. All recurrent AEs should be recorded individually on the AE CRF.

d. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs on the CRF and SAE form (if applicable). For example, abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.

If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs on the CRF and SAE form (if applicable), unless their severity, seriousness, or etiology changes.

e. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 12.4.1), regardless of attribution, will be recorded on the AE CRF and SAE form and reported to the Sponsor within 24 hours of event knowledge.

When recording a death, the event or condition that caused or contributed to the fatal outcome should be recorded as a single medical concept. For example, if death resulted from respiratory failure, the AE recorded should be "Respiratory Failure", and the Outcome of the AE would be "Death". If the cause of death is unknown and cannot be ascertained at the time of reporting, record "unexplained death" on the AE CRF and SAE form.

f. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical and Surgical History CRF.

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an AE CRF and SAE form (if applicable), it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

g. Pulmonary Exacerbation

Given the proposed mechanism of action of QR-010, it could be anticipated that subjects will experience a change in baseline cough, change in sputum quality, or change in sputum volume. A diagnosis of pulmonary exacerbation should be considered if these symptoms are accompanied by fever, body weight loss, generalized malaise. If a pulmonary exacerbation is diagnosed, appropriate interventions including additional antibiotics should be prescribed by the PI or treating physician. Subjects diagnosed with a pulmonary exacerbation requiring the addition of antibiotics will be withdrawn from the study.

h. Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

i. Pregnancy

If a female partner of a male subject in the study becomes pregnant while her partner is receiving investigational therapy or within 6 months after the last dose of study, a Pregnancy form should be completed and faxed to the Sponsor's Drug Safety Department or its designee within 24 hours of learning of the pregnancy, using the fax numbers listed in the Study Manual.

Abortion, whether therapeutic, or spontaneous, will be reported on a Pregnancy Report form and faxed to the Sponsor according to the instructions in the Study Manual. If the abortion meets seriousness criteria (see Section 12.5, Serious Adverse Event Definition), this information will be captured on the AE CRF and SAE form.

Any congenital anomaly/birth defect in a child born to a female subject or to a female partner of a male subject exposed to the investigational product should be recorded and reported as an SAE.

j. Overdose Reporting

Overdoses must be reported to the Sponsor on an AE CRF and an SAE form for tracking purposes and will be considered a protocol violation. Overdose is defined as any study drug dose administered above the intended dose for the cohort assignment. Additional instructions for reporting overdose information will be provided by the Sponsor at the time of notification.

12.5 Serious Adverse Event Definition

An SAE is any AE that suggests a significant hazard, contraindication, side effect, or precaution regardless of the relationship to study drug. An SAE is any AE that results in any of the following outcomes:

- Death
- Life-threatening AE. This definition implies that the subject, in the view of the Investigator, is at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- In-subject hospitalization or prolongs existing hospitalization, except for hospitalization for planned post-dose sample collections
- Persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- Congenital anomaly or birth defect. This serious criterion applies if a congenital anomaly/birth defect is diagnosed in a child born to a female subject, or a female partner of a male subject exposed to the investigational product.
- Other important medical events. Medical and scientific judgment should determine whether an AE should be classified as serious in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the outcomes listed in the definition above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependence or abuse.

All AEs that do not meet any of the criteria for serious should be regarded as **non-serious AEs.**

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the CRF and SAE form.

12.6 Suspected Unexpected Serious Adverse Reaction Definition

A SUSAR is a suspected unexpected serious adverse reaction. In order to be qualified as a SUSAR, the AE must meet 3 criteria: the event is serious, there is a certain degree of probability that the event is a reaction to the medical product being researched and the nature and severity of the reaction are not in agreement with the product information (ie, the reaction is unexpected as per the reference safety information). All SUSARs will be reported as required to the Competent Authorities of all involved European member states and to the Ethics Committee of the member states concerned.

12.7 Serious Adverse Events Notification

For all SAEs, regardless of suspected causality, an SAE form must be completed (or faxed if using paper form) within 24 hours of discovery of the event to:

DRUG SAFETY

Fax toll free: See Study Manual for Fax Number

Any fatal or life-threatening (ie, imminent risk of death) event that is attributed by the Investigator to the investigational product must be telephoned to Drug Safety immediately, followed by submission of written case details on an SAE form within 24 hours.

SAEs occurring any time after study participation that are considered by the Investigator to be possibly related to study drug must also be reported. The following are important points to remember when completing the SAE form:

- If complete information is not available, at a minimum, subject identifier, suspect drug, site identifier, event or outcome, and Investigator assessment of causal relationship to study drug should be provided.
- A rationale for the causality assessment of an SAE should always be included, so that a better understanding of the event can be compiled.

- Follow-up information, such as laboratory reports, discharge summaries, autopsy reports, and information concerning outcome of the event should be submitted by revising the SAE form as soon as the information becomes available. Copies of source documents with subject identifiers redacted should be submitted only when they are written in English. If source documents are not in English, the Investigator must summarize the source documents, providing a complete English narrative that includes a description of the events as it evolved, the results of all diagnostic procedures performed, treatments administered, and outcome of the event. A query regarding a follow-up report should be answered within 5 working days from receipt of the query.
- Appropriate diagnostic tests and therapeutic measures are to be performed as necessary and reported on the SAE form.
- All SAEs must be reported to the IRB/Independent Ethics Committee, if applicable. See ICH GCP E6, Section 4.11.1.

12.8 Expedited Reporting of SUSARs

- The Sponsor or its designee is responsible for notifying the investigational sites of all expedited SAEs (ie, 7/15 Day SUSARs) that occur during any clinical studies that are using the investigative compound. The Sponsor or its designee shall also notify Central Ethics Committees and Central IRB of SUSARs or significant risks to subjects, per country requirements. All SUSARs will be reported as required to the Competent Authorities of all involved European member states.
- The Investigator will notify local IRB or Local Ethics Committees (LECs) of SUSARs or significant risks to subjects, per local country requirements. The Investigator must keep copies of all AE information, including correspondence with the Sponsor or Local Ethics Committees on file.

  All studies that are conducted within any European country will comply with the European Clinical Trial Directive 2005/28/EC, the Clinical Trial Directive 2001/20/EC and the Detailed Guidance CT-3 (2011/C 172/01).

12.9 Emergency Unblinding Procedure

In the event of a medical emergency, when knowledge of treatment assignment is needed for immediate medical management of the subject's health, Investigators can obtain unblinded treatment assignment through the centralized IWRS system at any time. Thorough documentation of the rationale for unblinding is required. Consultation of the study Medical Monitor is recommended for all unblinding requests.

13.0 STATISTICAL METHODOLOGY

13.1 General Considerations

A comprehensive Statistical Analysis Plan (SAP) specifies the statistical methodology, and table, figure and listing (TLF) formats for all aspects of the planned analyses. The SAP supports the

completion of Clinical Study Report (CSR) for this protocol. As the risk profile of QR-010 in humans is unknown and this is a first in human trial, all AEs will be considered in determining the safety profile of QR-010 unless obviously unrelated. As an early phase clinical study, exploratory analyses not necessarily identified in the SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in the SAP will be clearly identified in the CSR, in accordance with applicable Standard Operating Procedures (SOPs) of the sponsor.

13.2 Determination of Sample Size

This is a Phase 1 safety study designed to evaluate the safety, tolerability and PK of QR-010. The sample size is not based on power calculations. It is chosen based on clinical experience and considered to be adequate to fulfill the objectives of the study.

Approximately 64 subjects will be enrolled in the study, with 8 subjects per cohort (6 QR-010 and 2 placebo), 32 each in the SAD and MAD portions of the study. The exact number of subjects enrolled is dependent on whether any dose level are to be expanded due to the occurrence of DLTs.

13.3 Randomization and Blinding

13.3.1 Randomization Procedures

At screening, potential subjects will be randomized into the current enrolling cohort. In the event that there is both a SAD and MAD cohort enrolling in parallel, the subject may elect participation in either an open SAD or MAD cohort. All sites will be capable of and expected to enroll all cohorts of the study. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for randomization. Eligible subjects will be randomized on Day -1 by a centralized interactive web response system (IWRS), utilizing the randomization schedule generated by the designated unblinded statistician. The IWRS system will be used to assign dose level and treatment assignments to subjects, within the cohort type (SAD or MAD) selected by the subject at screening.

Within each dosing cohort, subjects will be randomized 3:1, QR-010 to placebo. At least one of the first two subjects enrolled in the first cohort will be randomized to receive QR-010.

13.3.2 Blinding Procedures

Study drug will be administered in a double-blind fashion. Study drug and placebo are both clear, colorless, and odorless aqueous solutions. Subjects, Investigators and study site staff will be blinded to treatment assignment. However, due to the requirement for study pharmacists to prepare the various study drug dilutions depending on the dosing cohort to which a given study subject is assigned, the study pharmacist(s) will be unblinded to treatment assignment.

13.3.3 Replacement of Subjects

Subjects who discontinue from the study after randomization without receiving any treatment will be replaced. Subjects discontinuing the trial before the full course of treatment may be replaced by a subject who will be assigned the same treatment/dose as the subject being replaced. The decision for replacement will be made by the Sponsor based on available data and perceived need for additional data.

13.4 Analysis of Populations

Due to its exploratory nature, the analyses for this study will be mainly descriptive. If inferential statistics are provided they will be interpreated as hypothesis generation. Data analysis will be based on descriptive statistics for the dose groups, and when appropriate, pooled across dose groups. For continuous variables, the statistics include the following: geometric mean, mean, median, log-scale standard deviation, standard error of the mean, minimum and maximum. For categorical variables the statistics include frequency and proportions.

Screened: All subjects with an informed consent date will be part of this population.

Randomized: All subjects with a randomization date.

Safety Population: the population for safety analysis will consist of all subjects who receive any QR-010 or placebo. Subjects will be considered in the actual treatment received.

Exploratory Analysis Population: the population for efficacy (clinical activity) analysis will consist of all subjects randomized who receive at least one dose of QR-010 or placebo. Subjects will be considered in the actual treatment received.

Pharmacokinetics (PK) Population: will consist of all subjects who receive QR-010 and who have sufficient drug concentration measurements in blood samples or urine or sputum. This population will be used for PK analysis.

13.5 Subject Disposition, Demographics and Baseline Disease Characteristics

Subject disposition will be summarized for the safety population by dose group. The number and percentage of subjects enrolled in each site will be presented by geographic region (North America and Europe).

The number and percentage of subjects who receive QR-010 will be tabulated by the number of doses and the QR-010 dose group.

Subject demographics and baseline characteristics will be summarized for each dose group. Subject characteristics at baseline include age, race, body weight, and height. Baseline disease characteristics include pulmonary function (percent predicted), body weight, and CFQ-R

Respiratory Symptoms Score. The baseline data is defined as the data most recently collected prior to the first dose.

13.6 Treatment Compliance

All doses are observed and administered by study staff. Treatment compliance will be determined by source records documenting treatment observations and summarized.

13.7 Safety Analyses

13.7.1 Treatment Emergent Adverse Events

A treatment emergent AE (TEAE) is defined as an event that was not present prior to administration of the first dose of study drug and present after the first dose or if it represents the exacerbation of an event that was present prior to the first dose.

AEs noted during the study will be coded to system organ classes (SOCs) and preferred terms (PTs) using the MedDRA dictionary. The overall incidence of TEAEs will be summarized by dose group and classified by SOC and PT. Deaths, AE severity, seriousness, relationship to study drug and study discontinuation due to AE will also be tabulated by dose group. An AE will be considered drug-related if the Investigator indicated the event is at least "possibly" related or if the relationship is missing. AEs with missing start dates, but with stop dates overlapping into the treatment period will be counted as treatment emergent. All AEs will be listed in subject listing, and summarized by numbers and percents of subjects by dose for each portion of the study separately. If a subject reports the occurrence of a particular event more than once, the most severe of those events will be included in the summary tables of TEAEs, and the most severe of the treatment-related events will be included in the summary tables of treatment-related events.

13.7.2 Dose-Limiting Toxicities

Potential DLTs are reviewed and adjudicated by the DSMC. DLTs will be summarized by dose groups. Individual subject listings will be provided for each DLT including severity. Additional descriptive information such as associated laboratory values and action taken will be described in the clinical study report.

13.7.3 Vital Signs

Vital sign measurements will consist of respiratory rate, pulse, blood pressure, temperature and oximetry. Descriptive summaries (number of subjects, mean, standard deviation, median, minimum, and maximum) of actual values and changes from baseline will be presented for each time point. These summaries will be presented for the safety population and by dose group.

13.7.4 Laboratory Assessments

Laboratory measurements (hematology and chemistry) obtained at baseline and each study visit will be summarized by dose group, whenever possible, in the following ways:

- Descriptive statistics of actual results (number of subjects, mean, standard deviation, median, minimum, and maximum) for the continuous data and frequencies and percentages for the categorical data, for each time point
- Descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) of change from baseline to each time point
- Shift tables summarizing the frequencies of subjects below, within and above the normal ranges at baseline and to maximum and to minimum value during treatment and after treatment will be presented.
- Site local laboratories were used; summaries will be provided as units/ranges permit.

13.7.5 Other Safety Assessments

Other safety assessments, such as urinalysis, ECGs, and physical examinations will be summarized and listed as specified in the statistical analysis plan (SAP).

13.8 Pharmacokinetics Analyses

To determine the PK profile of inhaled administrations at the different dose levels of QR-010, the following PK parameters will be calculated if sufficient data are available for each dose:

- C_{max}: The maximum serum concentration will be taken directly from the data.
- T_{max}: Time to C_{max} will be taken directly from the data.
- $T_{½}$: The terminal elimination half-life will be estimated by non-linear regression analysis of the terminal elimination slope, if feasible.
- AUC_{0-t}: Area under the curve to the final sample with a concentration greater than lower limit of quantification (LLQ) will be calculated using the linear trapezoidal method.
- $AUC_{0-\infty}$: Area under the curve to infinity will be calculated based on the last observed concentration $C_{last}(obs)$ using formula: $AUC_{0-\infty}=AUC_{last}+C_{last}(obs)/\lambda z$, if feasible.
- CL: Serum clearance will be estimated using the formula: $CL = Dose/AUC_{0-\infty}$.

Achievement of steady state of the drug will be determined from trough levels.

Exact procedure for imputation of data will be described in the SAP.

All samples obtained from all cohorts will be analyzed to avoid bias in data presentation.

Sparse sampling analysis may be used to mitigate the risk of insufficient data to create individual profiles. The same approach may be used for non-compartmental analysis of sputum concentrations. This option provides the opportunity to characterize drug PK in CF patients as thoroughly as possible while keeping blood draws to a reasonable minimum for ethical considerations.

Correlation between concentrations in different matrices (serum, urine, sputum) may be explored.

Drug concentrations will be summarized by nominal time point if 3 or more values are available. Descriptive statistics for PK parameters will be performed if ≥ 50% of subjects have evaluable data and number of values to summarize is ≥ 3.

Geometric means and coefficients of variation will be tabulated for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and Cl for each dose group if possible. T_{max} will be summarized by median, minimum and maximum. Mean, standard deviation, minimum and maximum will be provided for $T_{½}$. Exact details for statistical analysis of PK concentrations and derived PK parameters will be presented in SAP.

13.9 Immunogenicity

For subjects with positive anti-QR-010 antibodies, the impact of the antibodies on the PK and safety of QR-010 will be evaluated.

13.10 Exploratory Efficacy Analyses

The exploratory clinical efficacy endpoints for the study will be evaluated for subjects enrolled in MAD cohorts. The exploratory efficacy evaluations will include:

- Pulmonary function
- Body weight
- CFQ-R RSS
- Sweat chloride

Descriptive statistics of clinical efficacy will be tabulated by dose group.

All continuous endpoints will be summarized using the following descriptive statistics: number of subjects, mean, standard deviation, standard error, median, minimum and maximum and 95% confidence intervals for the mean. Categorical endpoints will be summarized using: number of subjects, frequency, percentages and the 95% confidence intervals.

13.11 Interim Analysis

Safety will be assessed prior to each dose escalation by the DSMC.

For development purposes data analyses may be performed during the study.

13.12 Subgroup Analyses

No subgroup analyses are planned.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Changes to the Protocol

Protocol amendments must be made only with the prior approval of Sponsor. Sponsor will inform the Investigator in writing of any amendment to the protocol. The Investigator must submit the protocol modifications and any informed consent modifications to the IRB/IEC and applicable country authorities, and approval must be obtained before the modifications are implemented (unless a life threatening situation). The Investigator must send a copy of the approval letter from the IRB/IEC to the designated contract research organization (CRO) for Sponsor review.

Both the Sponsor and the Investigator reserve the right to terminate the study according to the study contract. The Investigator should notify the IRB/IEC and applicable country authorities in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

14.2 Data Collection and Study Monitoring

An electronic CRF (eCRF) will be used for this study. Study site personnel will be trained and authorized to use the system in compliance with the Code of Federal Regulations (CFR) 21CFR Part 11, ICH GCP and local regulations, before recording data on eCRFs. All corrections to eCRFs will be made by authorized users, and the changes will be automatically logged in the audit trail of the system (time and date stamps and the user entering or updating data).

eCRFs should be completed for every subject screened or enrolled in the study. Each subject will be identified by a unique subject identifier (site number and subject number). At the study's conclusion, a PDF file will be created for each site containing their subjects' data submitted on eCRFs. In the event of an audit or regulatory authority inspection, copies of the eCRFs will be printed.

The Investigator will ensure that the eCRFs are accurate, complete, and completed in a timely fashion. The Investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the eCRFs are never obliterated or destroyed. Separate source records are required to support all eCRF entries. The eCRF is not to be used to document data without prior written or electronic records.

To ensure the quality of clinical data across all subjects and sites, a clinical data management review will be performed on subject data. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for

adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries will be sent to the site. Corrections or updates to the data resulting from queries should be made on the eCRF. All changes will be automatically documented in the software's audit trail, including the reason for change.

The Investigator will electronically sign and date the indicated places on the eCRF. These signatures will indicate that the Investigator inspected or reviewed the data on the eCRF and agrees with the content.

A Sponsor representative will contact the Investigator(s) at periodic intervals by telephone or visit for the purpose of inspecting the facilities and assessing the progress of the study. CRFs, eCRFs, and subject records will be reviewed at on-site visits at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the CRFs and eCRF.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs/eCRF, are resolved.

Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. Study drug dispensing and accountability will also be assessed.

15.0 ETHICAL AND REGULATORY OBLIGATIONS

15.1 Ethical Considerations

The Investigator agrees to conduct this study in accordance with the ICH principles of GCP and with the Declaration of Helsinki (October 2013). The Investigator will conduct all aspects of this study in accordance with all national, state and local laws of the applicable regulatory agencies.

15.2 Informed Consent

Before the start of required study procedures, the Investigator or his/her associate must obtain informed consent from each study participant (or the subject's legal representative) in accordance with ICH GCP, the U.S. federal regulations (21 CFR Part 50) and corresponding country authority requirements. Separate informed consent may be required for CFTR genotyping, CFTR gene sequencing, and/or biomarker testing. The subject or his/her legal representative must sign the current version of the written, IRB/IEC-approved informed consent form in the presence of a witness and be given a copy. The Investigator will ensure that a copy of the signed consent is kept with the subject's records.

In accordance with ICH GCP and federal regulations (21 CFR 312.66), an IRB/IEC that complies with regulations in 21 CFR Part 56 must review and approve this protocol and the informed consent form prior to initiation of the study. The Investigator will submit a list of the names, occupations, and affiliations of the members of the IRB/IEC and documentation that the IRB/IEC is duly constituted or a General Assurance Number. No supplies will be shipped until the IRB/IEC and applicable country authorities have given written approval of the protocol and informed consent and the Sponsor has received copies of these approvals.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC and applicable country authorities for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IRB/IEC of deviations from the protocol or SAEs occurring at the site. SUSARs and other AE reports will be reported to the ECs and applicable country authorities by the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IRB/IEC renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB/IEC continuance of approval must be sent to the Sponsor.

Each U.S. IRB or corresponding regulatory authority participating in this clinical study is required to be registered with the U.S. Department of Health and Human Services (HHS) or corresponding agency respectively.

15.3 Pre-study Documentation Requirements

The Investigator is responsible for forwarding the following documents to the CRO for Sponsor review before the initial shipment of study drug to the site.

- Signed and dated protocol signature page (Investigator's Agreement)
- Copy of the IRB/IEC –approved informed consent form
- Copy of the IRB/IEC approval of the protocol
- Copy of applicable country authority approvals of the protocol
- Up-to-date curricula vitae of Investigator and all co/sub-investigators listed on Form FDA 1572
- The IRB/EC composition and/or written statement that the IRB/IEC is in compliance with regulations
- Laboratory normal ranges and documentation of laboratory certification (or equivalent)
- Signed study contract
- Completed FDA Form 1572 or Investigator Agreement
- Financial Disclosure Form

15.4 Subject Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained. On the CRFs or other documents submitted to the Sponsor, subjects should be identified by their date of birth and subject number only. For countries where local regulatory guidelines prohibit capture of full date of birth, partial date will be recorded in line with local regulations. Documents that are not for submission to the Sponsor (eg, signed informed consent forms), should be kept in strict confidence by the Investigator.

In compliance with federal and local regulations, it is required that the Investigator and institution permit authorized representatives of the Sponsor, the Food and Drug Administration, other regulatory authorities, and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any or all records and reports that are important to the evaluation of this study. The Investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to the study-related records without violating the confidentiality of the subject.

16.0 STUDY ADMINISTRATION

16.1 Good Clinical Practice and Regulatory Requirements

This study will be conducted in accordance with good clinical practices as described in the ICH E6 GCP, adopted 1 May 1996, and in accordance with CFR Parts 50, 56, 312, and 314. The ICH guideline may be obtained at the ICH web site:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf

Where applicable, this study must also be conducted in accordance with Directive 2001/20/EC of the European Parliament and of the Council of April 4, 2001 on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use.

16.2 Investigator's Brochure

Before the study begins, the Investigator will receive the QR-010 Investigator's Brochure describing all known contraindications, warnings, precautions, and adverse reactions associated with the administration of the study drug. If such information is revised while the study is in progress, the brochure will be amended or revised and the Sponsor will provide the most current version to the Investigator.

16.3 Protocol Amendments and Study Termination

Protocol amendments must be made only with the prior approval of Sponsor. Sponsor will inform the Investigator in writing of any amendment to the protocol. The Investigator must

submit the protocol modifications and any informed consent modifications to the IRB/IEC, and approval must be obtained before the modifications are implemented. The Investigator must send a copy of the approval letter from the IRB/IEC to the CRO for Sponsor to review.

Both the Sponsor and the Investigator reserve the right to terminate the study according to the study contract. The Investigator should notify the IRB/IEC in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

16.4 Study Documentation and Storage

The Sponsor will provide the Investigator with records of drug shipments, CRFs/eCRFs, and other forms as necessary. The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Subject files containing informed consents and supporting copies of source documentation. Any paper CRFs will also be contained in such a file.
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC, applicable country authorities, and the Sponsor
- Records of drug disposition and all drug-related correspondence.

In addition, all original source documents supporting entries in the CRFs/eCRFs must be maintained and be readily available.

Upon the request of the Sponsor, designees, or the regulatory authorities, the Investigator will make any and all study records available for inspection, including subject dairies and source documents. This information will be treated as confidential.

No study document is to be destroyed without prior written agreement between Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

16.5 Use of Information

All personal information pertaining to the subjects in this study and in any subsequent reports will be kept confidential. Subjects will be identified only by their date of birth and a subject number. It is the responsibility of the Investigator to keep a subject listing for cross-referencing.

The Investigator understands that the information developed in the clinical study will be used by the Sponsor in connection with the development of the study drug. This information may be

disclosed to other clinical Investigators, to the U.S. Food and Drug Administration (FDA), and to other government agencies.

16.6 End of Trial and Final Report

In North America, the Investigator or associate must notify the IRB/IEC when the study is closed and provide a final report to the IRB/IEC within 90 days of the last subject's completion of the study. If not initially provided by the Sponsor, a copy of this final report must also be provided to Sponsor or its representative.

In the EU, the Sponsor or its designee must notify the European Competent Authorities and ECs when the study is terminated, within 90 days of the last subject's completion of the study in the concerned country and/or worldwide in accordance with local requirements. In case of early termination, the deadline is 15 days. The Sponsor or its designee must provide a final report and/or synopsis to the European Competent Authorities and ECs at the latest 1 year after the study termination worldwide, in accordance with local requirements. A copy of this final report and associated synopsis must also be provided to the Investigator.

16.7 Financing and Insurance

Financing and Insurance are addressed separately in the Clinical Study Agreement.

16.8 Publication Policy

The publications policy is also provided in the Clinical Study Agreement. The data from this study will be available to the Investigators for publication upon the completion of the study. The Sponsor agrees to have the results published, whether positive or negative. A publication committee will be formed composed of the Investigators. The Sponsor will review any manuscripts to ensure that proprietary information has the appropriate patent protection prior to journal submission.

17.0 REFERENCES

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18.0 APPENDICES

Appendix 1 Schedule of Assessments

Appendix 2 Schedule of Laboratory Assessments

Appendix 3 CFQ-R, Adult Version (English)

APPENDIX 1: SCHEDULE OF ASSESSMENTS

Table A.1-1: Single Ascending Dose Cohorts 1-4

Study Procedures	Screening	Check-In				Discharge				End of Study
Study Day	**≤-14 days[a]**	**-1**	**1[b]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
In Hours		**-24**	**0**	**24**	**48**	**72**	**96**	**120**	**144**	**168**
Informed consent	X									
Demographics	X									
Medical History	X									
Eligibility Review	X	X								
Concomitant Medications	X	X	X	X	X	X				X
Adverse Events		X	X	X	X	X				X
Physical Exam	C	C	S	S		S				C
Height & Weight	H/W	W	W							W
Vital Signs[c] & Oximetry	X	X	X	X	X	X				X
Spirometry[d]	X	X	X	X		X				X
Chest Xray	X[e]									X[f]
12-lead ECG	X									X
24-Hour Telemetry			X							
Blood for Safety Labs[g]	X	X[h]	X	X	X	X				X
Urinalysis[g]	U	U[h]	U	U	U	U				U
Drug Screen[g]	X									
Pregnancy Test[g,i]	X	X								X
Sputum for Microbiology[g]		X								X
Blood for CFTR[g]	Genotyping	Sequencing								
Biomarkers[g]	X	X		X		X				X
Sweat Chloride[g]	X									
Randomization		X								
Study Drug Administration[j]			X							
Collect Samples for PK[g]			X	X	X	X				X

Abbreviations: C = complete physical exam; H = height; S = symptom-directed physical exam; U = urinalysis (dipstick); W = weight

[a] The screening period for an individual subject may be extended for an additional 7 days at the discretion of the Sponsor's Medical Monitor. See Section 7.2 for details.
[b] See Section 7.3.2 for details on timing of these assessments relative to study drug administration on Day 1.
[c] Includes blood pressure, heart rate, respiratory rate, and temperature.
[d] Includes FEV_1, FVC, and FEF_{25-75}.
[e] A Chest Xray or CT scan obtained within 90 days of screening is acceptable if there was no intercurrent pulmonary illness during the interim.
[f] Only subjects who experience pulmonary AEs during the study.
[g] See Appendix 2 for a detailed schedule of these assessments, broken down by type of specimen and time relative to dose.
[h] Only laboratory assessments that are abnormal (but not clinically significant) at screening should be repeated at Day-1.
[i] Pregnancy test (preferably serum but urine is accepted) required for women of childbearing potential only.
[j] Subjects who are taking concurrent CF therapy should receive this therapy prior to study drug dosing in the order specified in Section 6.3.1.

Table A.1-2: Multiple Ascending Dose Cohorts 5-8, WEEK 1

Dosing Schedule assumes Monday-Wednesday-Friday dosing:

Study Procedures	**Screening**		**Dose 1**	**Dose 2**		**Dose 3**		
Study Day	**≤-14 days[a]**	**-1**	**1**	**3**	**4**	**5**	**6**	**7**
In Hours Post Dose 1		**-24**	**0**	**48**	**72**	**96**	**120**	**144**
Informed consent	X							
Demographics	X							
Medical History	X							
Eligibility Review	X	X						
Concomitant Medications	X	X	X	X	X	X		
Adverse Events		X	X	X	X	X		
Physical Exam	C	C	S	S	S	S		
Height & Weight	H/W	W	W					
Vital Signs[b] & Oximetry	X	X	X	X	X	X		
Spirometry[c]	X	X	X	X	X	X		
Chest Xray	X[d]							
12-lead ECG	X							
Telemetry			X					
CFQ-R RSS[e]			X					
Blood for Safety Labs[f]	X	X[g]	X	X	X			
Urinalysis[f]	U	U[g]	U	U	U			
Drug Screen[f]	X							
Pregnancy Test[f,h]	X	X						
Sputum for Microbiology[f]		X						
Blood for CFTR[f]	Genotyping	Sequencing						
Biomarkers[f]	X	X			X			
Sweat Chloride[f]	X							
Randomization		X						
Study Drug Administration[i]			X	X		X		

Study Procedures	Screening		Dose 1	Dose 2		Dose 3		
Collect Samples for PK[f]			X	X	X	X		

Abbreviations: C = complete physical exam; CFQ-R RSS = Cystic Fibrosis Questionnaire-Revised Respiratory Symptom Score; ECG = electrocardiogram; H = height; PK = pharmacokinetic; S = symptom-directed physical exam; U = urinalysis (dipstick); W = weight

NOTE: See also Section 7.4 for details on timing of assessments relative to study drug administration.

[a] The screening period for an individual subject may be extended for an additional 7 days at the discretion of the Sponsor's Medical Monitor. See Section 7.2 for details.
[b] Includes blood pressure, heart rate, respiratory rate, and temperature.
[c] Includes FEV_1, FVC, and FEF_{25-75}.
[d] A Chest Xray or CT scan obtained within 90 days of screening is acceptable if there was no intercurrent pulmonary illness during the interim.
[e] Should be completed prior to any other procedures or assessments.
[f] See Appendix 2 for a detailed schedule of these assessments, broken down by type of specimen and time relative to dose.
[g] Only laboratory assessments that are abnormal (but not clinically significant) at screening should be repeated at Day-1.
[h] Pregnancy test (preferably serum but urine is accepted) required for women of childbearing potential only.
[i] Subjects who are taking concurrent CF therapy should receive this therapy prior to study drug dosing in the order specified in Section 6.3.1.

Table A.1-3: Multiple Ascending Dose Cohorts 5-8, WEEK 2

Study Procedures	Dose 4		Dose 5		Dose 6		
Study Day	**8**	**9**	**10**	**11**	**12**	**13**	**14**
In Hours Post Dose 1	**168**	**192**	**216**	**240**	**264**	**288**	**312**
Concomitant Medications	X		X		X		
Adverse Events	X		X		X		
Physical Exam	C/S		S		S		
Height & Weight	W						
Vital Signs[a] & Oximetry	X		X		X		
Spirometry[b]	X						
Blood for Safety Labs[c]	X						
Urinalysis[c]	U						
Biomarkers[c]	X						
Study Drug Administration[d]	X		X		X		
Collect Samples for PK[c]	X		X		X		

Abbreviations: C = complete physical exam; PK = pharmacokinetic; S = symptom-directed physical exam; U = urinalysis (dipstick); W = weight

NOTE: See also Section 7.4 for details on timing of assessments relative to study drug administration.

[a] Includes blood pressure, heart rate, respiratory rate, and temperature.

[b] Includes FEV_1, FVC, and FEF_{25-75}.

[c] See Appendix 2 for a detailed schedule of these assessments, broken down by type of specimen and time relative to dose.

[d] Subjects who are taking concurrent CF therapy should receive this therapy prior to study drug dosing in the order specified in Section 6.3.1.

Table A.1-4: Multiple Ascending Dose Cohorts 5-8, WEEK 3

Study Procedures	Dose 7		Dose 8		Dose 9		
Study Day	**15**	**16**	**17**	**18**	**19**	**20**	**21**
In Hours Post Dose 1	**336**	**360**	**384**	**408**	**432**	**456**	**480**
Concomitant Medications	X		X		X		
Adverse Events	X		X		X		
Physical Exam	C/S		S		S		
Height & Weight	W						
Vital Signs[a] & Oximetry	X		X		X		
Spirometry[b]	X						
CFQ-R RSS[c]	X						
Blood for Safety Labs[d]	X						
Urinalysis[d]	U						
Biomarkers[d]	X						
Study Drug Administration[e]	X		X		X		
Collect Samples for PK[d]	X		X		X		

Abbreviations: C = complete physical exam; CFQ-R RSS = Cystic Fibrosis Questionnaire-Revised Respiratory Symptom Score; PK = pharmacokinetic; S = symptom-directed physical exam; U = urinalysis (dipstick); W = weight

NOTE: See also Section 7.4 for details on timing of assessments relative to study drug administration.

[a] Includes blood pressure, heart rate, respiratory rate, and temperature.

[b] Includes FEV_1, FVC, and FEF_{25-75}.

[c] Should be completed prior to any other procedures or assessments.

[d] See Appendix 2 for a detailed schedule of these assessments, broken down by type of specimen and time relative to dose.

[e] Subjects who are taking concurrent CF therapy should receive this therapy prior to study drug dosing in the order specified in Section 6.3.1.

Table A.1-5: Multiple Ascending Dose Cohorts 5-8, WEEK 4

Study Procedures	Dose 10		Dose 11		Dose 12
Study Day	**22**	**23**	**24**	**25**	**26**
In Hours Post Dose 1	**504**	**528**	**552**	**576**	**600**
Concomitant Medications	X		X		X
Adverse Events	X		X		X
Physical Exam[a]	C/S		S		C/S
Height & Weight	W				W
Vital Signs[b] & Oximetry[a]	X		X		X
Spirometry[a,c]	X				X
Blood for Safety Labs[d]	X				
Urinalysis[d]	U				
Biomarkers[d]	X				
Sweat Chloride[d]					X
Study Drug Administration[e]	X		X		X
Collect Samples for PK[d]	X		X		X

Abbreviations: C = complete physical exam; PK = pharmacokinetic;
S = symptom-directed physical exam; U = urinalysis (dipstick); W = weight

[a] See Section 7.4 for details on timing of these assessments relative to study drug administration.

[b] Includes blood pressure, heart rate, respiratory rate, and temperature.

[c] Includes FEV_1, FVC, and FEF_{25-75}.

[d] See Appendix 2 for a detailed schedule of these assessments, broken down by type of specimen and time relative to dose.

[e] Subjects who are taking concurrent CF therapy should receive this therapy prior to study drug dosing in the order specified in Section 6.3.1.

Table A.1-6: Multiple Ascending Dose Cohorts 5-8, Follow-Up Visits

Study Procedures	PK Follow-up 24 Hours After Last Dose	PK Follow-up 96 Hours After Last Dose	7 Days After Last Dose (End of Treatment)	Follow-up 28 Days after Last Dose (End of Study)
Study Day	**27 ± 1**	**30 ± 2**	**33**	**54**
In Hours Post Dose 1	**624 ± 12**	**696 ± 48**	**768**	**1272**
Concomitant Medications			X	X
Adverse Events			X	X
Physical Exam			C	C
Height & Weight			W	W
Vital Signs[a] & Oximetry			X	X
Spirometry[b]			X	X
Chest Xray			X	
12-lead ECG			X	
CFQ-R RSS[c]			X	X
Blood for Safety Labs[d]			X	X
Urinalysis[d]			U	U
Pregnancy test[d,e]			X	X
Sputum for Microbiology[d]			X	
Biomarkers[d]			X	X
Sweat Chloride[d]			X	X
Collect Samples for PK[d]	X	X	X	X

Abbreviations: C = complete physical exam; CFQ-R RSS = Cystic Fibrosis Questionnaire-Revised Respiratory Symptom Score; PK = pharmacokinetic;U = urinalysis (dipstick); W = weight

[a] Includes blood pressure, heart rate, respiratory rate, and temperature.

[b] Includes FEV_1, FVC, and FEF_{25-75}.

[c] Should be completed prior to any other procedures or assessments.

[d] See Appendix 2 for a detailed schedule of these assessments, broken down by type of specimen and time relative to dose.

[e] Pregnancy test (preferably serum but urine is accepted) required for women of child-bearing potential only.

APPENDIX 2: SCHEDULE OF LABORATORY TESTS

Table A.2-1: Single Ascending Dose Cohorts 1-4

Labs	Screening	Check-In	Dose			Discharge				End of Study[a]
Study Day	**≤-14 days[b]**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
In Hours		**-24**	**0**	**24**	**48**	**72**	**96**	**120**	**144**	**168**
Hematology	X	X	X	X	X	X				X
Serum Chemistry	X	X	X	X	X	X				X
Hematology & Chemistry	Day 1: Pre-dose, 30, 60 minutes, 2, 4, 8, 12 hours post dose									
C-Reactive Protein		X	X	X						X
Erythrocyte Sedimentation Rate		X	X	X						X
C-Reactive Protein & Erythrocyte Sedimentation Rate	Day -1 Day 1: Pre-dose, 24 hours post dose									
Coagulation and CH50	X									X
Direct Antiglobulin Test	X									X
Serum Tocopherol (Vit. E)	X									
Urine microalbumin		X								X
Urinalysis	X	X	X	X	X	X				X
	Day 1: On pooled PK samples Day 2, 3, 4, 8: Random sample, preferably 1st morning void									
Drug Screen	X[c]									
Pregnancy test[d]	X	X								X
Sputum for Microbiology		X								X
CFTR Genotyping[e]	X									
CFTR Sequencing		X[f]								
Sweat Chloride	X									
PK Sampling	Serum: 0, 0.5, 1, 2, 3, 4, 12, 24, 48, 54, 72, 168 hours post dose Urine: Pre-dose; Pooled from 0 to 4, 4 to 12, and 12 to 24 hours post-dose; and 48, 72, and 168 hours post dose (UA on each pooled sample). Sputum: 3 samples obtained within first 6 hours post dose; 24 hours post dose; Day 4 (72 hours post dose); and Day 8 (168 hours post dose)									
Serum for PK			X	X	X	X				X
Urine for PK			X	X	X	X				X
Sputum for PK			X[g]	X		X[h]				X[g]

Labs	Screening	Check-In	Dose			Discharge				End of Study[a]
Biomarker Sampling										
Blood (serum and plasma) for Biomarkers	X	X[g]		X		X				X
Sputum for Biomarkers	X	X[g]		X		X				X

[a] For subjects who withdraw prematurely from the study, this visit will occur whenever they leave the study.

[b] The screening period for an individual subject may be extended for an additional 7 days at the discretion of the Sponsor's Medical Monitor. See Section 7.2 for details.

[c] Drug screening may be performed on urine or blood sample.

[d] Women of child-bearing potential only

[e] Required if original documentation for CF genotyping is not available or is earlier than the year 2000.

[f] Samples may be collected on Day 1 pre-dose instead of Day -1.

[g] Suggest obtaining samples in conjunction with performing spirometry at 10, 60 minutes, and 4 hours post dose.

[h] Sample may be taken any time prior to discharge (Day 4) or during visit (End of Study).

Table A.2-2: Multiple Ascending Dose Cohorts 5-8, WEEK 1

Dosing Schedule assumes Monday-Wednesday-Friday dosing:

Study Procedures	Screening		Dose 1	Dose 2		Dose 3		
Study Day	**≤-14 days[a]**	**-1**	**1**	**3**	**4**	**5**	**6**	**7**
In Hours		**-24**	**0**	**48**	**72**	**96**	**120**	**144**
Hematology	X	X	X	X	X			
Serum Chemistry	X	X	X	X	X			
Hematology & Chemistry	Dose 1: Pre-dose, 30, 60 minutes, 2, 4, 8, 12 hours post Dose 1 Dose 2: 60 minutes and 4 hours post Dose 2							
C-Reactive Protein		X	X					
Erythrocyte Sedimentation Rate		X	X					
C-Reactive Protein & Erythrocyte Sedimentation Rate	Day -1 Day 1: Pre-dose							
Coagulation and CH50	X							
Direct Antiglobulin Test	X							
Serum Tocopherol (Vit. E)	X							
Urine microalbumin		X						
Urinalysis	X	X	X	X	X			
	Dose 1: Pre-dose, 0-4, 4-12 hours post dose (UA on each pooled sample) Dose 2: 60 minutes and 4 hours post dose							
Drug Screen	X[b]							
Pregnancy Test[c]	X	X						
Sputum for Microbiology		X						
CFTR Genotyping[d]	X							
CFTR Sequencing		X[e]						
Sweat Chloride	X							
PK Sampling	Serum: 0, 0.5, 1, 2, 3, 4, 12; pre-Dose 2; 2 hours post Dose 2; 72 hours post Dose 1; 96 hours post Dose 1 (pre-Dose 3) Urine: Pre-dose; Pooled from 0 to 4 and 4 to 12 hours post Dose 1 (UA on each pooled sample). A separate sample should be collected at 72 hours post Dose 1. Sputum: 3 samples obtained within first 6 hours post Dose 1 and Day 4 (72 hours)							
Serum for PK			X	X	X	X		
Urine for PK			X		X			
Sputum for PK			X[f]		X			
Biomarker Sampling								
Blood (serum and plasma) for Biomarkers	X	X[e]			X			
Sputum for Biomarkers	X	X[e]			X			

[a] The screening period for an individual subject may be extended for an additional 7 days at the discretion of the Sponsor's Medical Monitor. See Section 7.2 for details.
[b] Drug screening may be performed on urine or blood sample.
[c] Women of child-bearing potential only.
[d] Required if original documentation for CF genotyping is not available or is earlier than the year 2000.
[e] Samples may be collected on Day 1 pre-dose instead of Day -1. Samples for CFTR sequencing should not be collected for subjects who participated in SAD cohort.
[f] Suggest obtaining samples in conjunction with performing spirometry at 10, 60 minutes, and 4 hours post dose.

Table A.2-3: Multiple Ascending Dose Cohorts 5-8, WEEK 2

Labs	**Dose 4**		**Dose 5**		**Dose 6**		
Study Day	**8**	**9**	**10**	**11**	**12**	**13**	**14**
In Hours	**168**	**192**	**216**	**240**	**264**	**288**	**312**
Hematology	X						
Serum Chemistry	X						
Hematology & Chemistry	Dose 4: Pre-dose, 15, 60 minutes, 2 hours post dose						
C-Reactive Protein	X						
Erythrocyte Sedimentation Rate	X						
C-Reactive Protein & Erythrocyte Sedimentation Rate	Dose 4: Pre-dose						
Coagulation and CH50	X						
Urinalysis	X						
	Dose 4: Pre-dose, 60 minutes and 2 hours post dose						
PK Sampling	Serum: Prior to Dose 4, 5, and 6 Sputum: Prior to Doses 4, 5, and 6						
Serum for PK	X		X		X		
Sputum for PK	X		X		X		
Biomarker Sampling	Dose 4: Pre-dose						
Blood (serum and plasma) for Biomarkers	X						
Sputum for Biomarkers	X						

Table A.2-4: Multiple Ascending Dose Cohorts 5-8, WEEK 3

Study Procedures	**Dose 7**		**Dose 8**		**Dose 9**		
Study Day	**15**	**16**	**17**	**18**	**19**	**20**	**21**
In Hours	**336**	**360**	**384**	**408**	**432**	**456**	**480**
Hematology	X						
Serum Chemistry	X						
Hematology & Chemistry	Dose 7: Pre-dose, 15, 60 minutes, 2 hours post dose						
C-Reactive Protein	X						
Erythrocyte Sedimentation Rate	X						
C-Reactive Protein & Erythrocyte Sedimentation Rate	Dose 7: Pre-dose						
Urinalysis	X						
	Dose 7: Pre-dose, 60 minutes and 2 hours post dose						
PK Sampling	Serum: Prior to Dose 7, and 1 hours post Dose 7; Prior to Doses 8 and 9						
Serum for PK	X		X		X		
Biomarker Sampling	Dose 7: Predose						
Blood (serum and plasma) for Biomarkers	X						
Sputum for Biomarkers	X						

Table A.2-5: Multiple Ascending Dose Cohorts 5-8, WEEK 4

Study Procedures	Dose 10		Dose 11		Dose 12
Study Day	**22**	**23**	**24**	**25**	**26**
In Hours	**504**	**528**	**552**	**576**	**600**
Hematology	X				
Serum Chemistry	X				
Hematology & Chemistry	Dose 10: Pre-dose, 15, 60 minutes, 2 hours post dose				
C-Reactive Protein	X				
Erythrocyte Sedimentation Rate	X				
C-Reactive Protein & Erythrocyte Sedimentation Rate	Dose 10: Pre-dose				
Urine microalbumin	X				
Urinalysis	X				
	Dose 10: Urine microalbumin pre-dose Dose 10: Urinalysis pre-dose, 60 minutes and 2 hours post dose				
Sweat Chloride					X
PK Sampling	Serum: Pre-Dose 10 and 11; Dose 12 (pre-dose; post dose at 1, 2, 3, 4, 8 hours) Urine: Dose 12 pre-dose only				
Serum for PK	X		X		X
Urine for PK					X
Biomarker Sampling	Dose 10: Pre-dose				
Blood (serum and plasma) for Biomarkers	X				
Sputum for Biomarkers	X				

Table A.2-6: Multiple Ascending Dose Cohorts 5-8, Follow-up

Study Procedures	PK Follow-up 24 hours After Last Dose	PK Follow-up 96 Hours After Last Dose	7 Days After Last Dose (End of Treatment)[a]	28 Days After Last Dose (End of Study)[a]
Study Day	**27**	**30**	**33**	**54**
In Hours Post Dose 1	**624 ± 12**	**696 ± 96**	**768**	**1272**
Hematology			X	X
Serum Chemistry			X	X
C-Reactive Protein			X	
Erythrocyte Sedimentation Rate			X	
Coagulation and CH50			X	
Direct Antibody Test			X	
Urine microalbumin				X
Urinalysis			X	X
Pregnancy test[b]			X	X
Sputum for Microbiology			X	
Sweat Chloride			X	X
PK Sampling	Serum post last dose: 24 ±12 hrs, 96 ± 48, hours post last dose, and at End of Treatment and End of Study Visit Urine post last dose: 24 ±12 hrs, 96 ± 48, hours post last dose			
Serum for PK	X	X	X	X
Urine for PK	X	X		
Biomarker Sampling	End of Treatment and End of Study Visits			
Blood (serum and plasma) for Biomarkers			X	X
Sputum for Biomarkers			X	X

[a] See Section 5.5.2 for details on these visits for subjects who withdraw prematurely from the study.

[b] Women of child-bearing potential only

APPENDIX 3: ADULT CFQ-R (ENGLISH)

CFQ-R **Adolescents and Adults (Patients 14 Years Old and Older)**
CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Understanding the impact of your illness and treatments on your everyday life can help your healthcare team keep track of your health and adjust your treatments. For this reason, this questionnaire was specifically developed for people who have cystic fibrosis. Thank you for your willingness to complete this form.

Instructions: The following questions are about the current state of your health, as you perceive it. This information will allow us to better understand how you feel in your everyday life.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Section I. Demographics

Please fill-in the information or check the box indicating your answer.

A. What is your date of birth?
Date ☐☐ ☐☐ ☐☐☐☐
Mo Day Year

B. What is your gender?
☐ Male ☐ Female

C. During the **past two weeks**, have you been on vacation or out of school or work for reasons **NOT** related to your health?

☐ Yes ☐ No

D. What is your current marital status?
- ☐ Single/never married
- ☐ Married
- ☐ Widowed
- ☐ Divorced
- ☐ Separated
- ☐ Remarried
- ☐ With a partner

E. Which of the following best describes your racial background?
- ☐ Caucasian
- ☐ African American
- ☐ Hispanic
- ☐ Asian/Oriental or Pacific Islander
- ☐ Native American or Native Alaskan
- ☐ Other (please describe) _____
- ☐ Prefer not to answer this question

F. What is the highest grade of school you have completed?
- ☐ Some high school or less
- ☐ High school diploma/GED
- ☐ Vocational school
- ☐ Some college
- ☐ College degree
- ☐ Professional or graduate degree

G. Which of the following best describes your current work or school status?
- ☐ Attending school outside the home
- ☐ Taking educational courses at home
- ☐ Seeking work
- ☐ Working full or part time (either outside the home or at a home-based business)
- ☐ Full time homemaker
- ☐ Not attending school or working due to my health
- ☐ Not working for other reasons

CFQ-R **Adolescents and Adults (Patients 14 Years Old and Older)**
CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Section II. Quality of Life

Please check the box indicating your answer.

*During the past **two weeks**, to what extent have you had difficulty:*	**A lot of difficulty**	**Some difficulty**	**A little difficulty**	**No difficulty**
1. Performing vigorous activities such as running or playing sports	☐	☐	☐	☐
2. Walking as fast as others	☐	☐	☐	☐
3. Carrying or lifting heavy things such as books, groceries, or school bags	☐	☐	☐	☐
4. Climbing one flight of stairs	☐	☐	☐	☐
5. Climbing stairs as fast as others	☐	☐	☐	☐

***During the past two weeks**, indicate how often:*	**Always**	**Often**	**Sometimes**	**Never**
6. You felt well	☐	☐	☐	☐
7. You felt worried	☐	☐	☐	☐
8. You felt useless	☐	☐	☐	☐
9. You felt tired	☐	☐	☐	☐
10. You felt energetic	☐	☐	☐	☐
11. You felt exhausted	☐	☐	☐	☐
12. You felt sad	☐	☐	☐	☐

Please circle the number indicating your answer. Please choose only one answer for each question.

*Thinking about the state of your health over the last **two weeks**:*

13. To what extent do you have difficulty walking?
1. You can walk a long time without getting tired
2. You can walk a long time but you get tired
3. You cannot walk a long time because you get tired quickly
4. You avoid walking whenever possible because it's too tiring for you

14. How do you feel about eating?
1. Just thinking about food makes you feel sick
2. You never enjoy eating
3. You are sometimes able to enjoy eating
4. You are always able to enjoy eating

15. To what extent do your treatments make your daily life more difficult?
1. Not at all
2. A little
3. Moderately
4. A lot

Adolescents and Adults (Patients 14 Years Old and Older)

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

16. How much time do you currently spend each day on your treatments?
1. A lot
2. Some
3. A little
4. Not very much

17. How difficult is it for you to do your treatments (including medications) each day?
1. Not at all
2. A little
3. Moderately
4. Very

18. How do you think your health is now?
1. Excellent
2. Good
3. Fair
4. Poor

Please select a box indicating your answer.

*Thinking about your health during the past **two weeks**, indicate the extent to which each sentence is true or false for you.*	**Very true**	**Somewhat true**	**Somewhat false**	**Very false**
19. I have trouble recovering after physical effort	☐	☐	☐	☐
20. I have to limit vigorous activities such as running or playing sports	☐	☐	☐	☐
21. I have to force myself to eat	☐	☐	☐	☐
22. I have to stay at home more than I want to	☐	☐	☐	☐
23. I feel comfortable discussing my illness with others	☐	☐	☐	☐
24. I think I am too thin	☐	☐	☐	☐
25. I think I look different from others my age	☐	☐	☐	☐
26. I feel bad about my physical appearance	☐	☐	☐	☐
27. People are afraid that I may be contagious	☐	☐	☐	☐
28. I get together with my friends a lot	☐	☐	☐	☐
29. I think my coughing bothers others	☐	☐	☐	☐
30. I feel comfortable going out at night	☐	☐	☐	☐
31. I often feel lonely	☐	☐	☐	☐
32. I feel healthy	☐	☐	☐	☐
33. It is difficult to make plans for the future (for example, going to college, getting married, advancing in a job, etc.)	☐	☐	☐	☐
34. I lead a normal life	☐	☐	☐	☐

CFQ-R **Adolescents and Adults** (Patients 14 Years Old and Older)
CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Section III. School, Work, or Daily Activities

Questions 35 through 38 are about school, work, or other daily tasks.

35. To what extent did you have trouble keeping up with your schoolwork, professional work, or other daily activities during the past **two weeks**?
1. You have had no trouble keeping up
2. You have managed to keep up but it's been difficult
3. You have been behind
4. You have not been able to do these activities at all

36. How often were you absent from school, work, or unable to complete daily activities during the last two weeks because of your illness or treatments?
☐ Always ☐ Often ☐ Sometimes ☐ Never

37. How often does CF get in the way of meeting your school, work, or personal goals
☐ Always ☐ Often ☐ Sometimes ☐ Never

38. How often does CF interfere with getting out of the house to run errands such as shopping or going to the bank?
☐ Always ☐ Often ☐ Sometimes ☐ Never

Section IV. Symptom Difficulties

Please select a box indicating your answer.

*Indicate how you have been feeling during the past **two weeks**.*	**A great deal**	**Somewhat**	**A little**	**Not at all**
39. Have you had trouble gaining weight?	☐	☐	☐	☐
40. Have you been congested?	☐	☐	☐	☐
41. Have you been coughing during the day?	☐	☐	☐	☐
42. Have you had to cough up mucus?	☐	☐	☐	☐ Go to Question 44

43. Has your mucus been mostly: ☐ Clear ☐ Clear to yellow ☐ Yellowish-green ☐ Green with traces of blood ☐ Don't know

*How often during the past **two weeks**:*	**Always**	**Often**	**Sometimes**	**Never**
44. Have you been wheezing?	☐	☐	☐	☐
45. Have you had trouble breathing?	☐	☐	☐	☐
46. Have you woken up during the night because you were coughing?	☐	☐	☐	☐
47. Have you had problems with gas?	☐	☐	☐	☐
48. Have you had diarrhea?	☐	☐	☐	☐
49. Have you had abdominal pain?	☐	☐	☐	☐
50. Have you had eating problems?	☐	☐	☐	☐

Please be sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

Cystic Fibrosis Foundation