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STATISTICAL ANALYSIS PLAN

Protocol PQ-010-001

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 Number: **(Version Date)**	PQ-010-001 Version 8.0, 04 April 2017, Version 8.1, 5 April 2017, Version 8.2, 5 April 2017
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Phase:	1b
Methodology:	Randomized, double-blind, 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)
Sponsor:	ProQR Therapeutics Zernikedreef 9 2333 CK Leiden The Netherlands
Sponsor Representative:	[redacted] VP Clinical Development and Study Medical Monitor
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SIGNATURE PAGE

Protocol Title:	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
Sponsor:	ProQR Therapeutics Zernikedreef 9 2333 CK Leiden The Netherlands
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[redacted] **Author:**
Director, Biostatistics
[redacted]

Signature:_____
Date:_____

[redacted] **Author:**
Associate Director, Quantitative Pharmacology & Pharmacometrics
[redacted]

Signature:_____
Date:_____

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatory: [redacted] Clinical Trial Manager ProQR Therapeutics Zernikedreef 9 2333 CK Leiden The Netherlands	Signature:_____ Date:_____
[redacted] VP Clinical Development and Study Medical Monitor ProQR Therapeutics Zernikedreef 9 2333 CK Leiden The Netherlands	Signature:_____ Date:_____
[redacted] VP Program Development ProQR Therapeutics Zernikedreef 9 2333 CK Leiden The Netherlands	Signature:_____ Date:_____

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
Ae	Amount of QR-010 excreted unchanged in the urine
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUCinf	Area under the concentration-time curve from time 0 extrapolated to infinite
AUClast	Area under the concentration-time curve from time 0 to the last quantifiable time point
AUCtau	Area under the concentration-time curve from time 0 to the end of the dosing interval tau.
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CF	Cystic Fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFQ-R RSS	CFQ-R Respiratory Symptoms Score
CH50	Total hemolytic complement
Cl/F	Apparent clearance
Clr	Renal Clearance
Cmax	Maximum concentration observed during a dosing interval
CRF	Case Report Form
CRP	C-Reactive Protein
CSR	Clinical Study Report
Css	Steady-State QR-010 concentration
Ctrough	Concentration of QR-010 observed just prior to administering a multiple dose
DSMC	Data Safety Monitoring Committee
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED50	Median effective dose
EOT	End Of Treatment
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
fe%	Fraction of QR-010 dose excreted unchanged in the urine
FEF	Forced Expiratory Flow

Abbreviation	Definition
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GGT	Gamma-Glutamyl Transferase
HGB	Hemoglobin
hr	hour
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IWRS	Interactive Web Response System
Lambda z (λz)	Terminal elimination rate constant
lb	pound
LDH	Lactacte Dehydrogenase
MAD	Multiple Ascending Doses
MedDRA	Medical Dictionary for Regulatory Activities
MCPMOD	Multiple Comparison Procedure Modelling
mmol/L	Millimole per Liter
MTD	Maximal Tolerated Dose
PK	Pharmacokinetic
$ppFEV_1$	Percent Predicted Forced Expiratory Volume in 1 second
PT	Prothrombin Time / Preferred Term
Ro	Accumulation ratio based on total systemic exposure
Ro,Cmax	Accumulation ratio based on maximal systemic exposure
SAD	Single Ascending Dose
SAP	Statistical Analysis Plan
SOC	System Organ Class
Tmax	Time of maximum concentration observed during a dosing interval
$T_{1/2}$	Elimination half-life
V/F	Apparent volume of distribution
WHO	World Health Organization

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

The study is a multicenter, randomized, double-blind, and placebo-controlled Phase 1b single ascending dose-escalation (SAD) followed by a multiple ascending dose-escalation (MAD). Eligible subjects with homozygous ΔF508 Cystic Fibrosis (CF) were to be randomized at a 3:1 ratio to receive either QR-010 or placebo vial oral inhalation (nebulization).

The study includes 2 parts. 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.

This study comprises intermediate analyses reviewed by an independent Data Safety Monitoring Committee (DSMC). The DSMC provides recommendation for dose escalation.

This document refers to Protocol No. PQ-010-001 version 8.0, 04 April 2017, version 8.1, 5 April 2017, version 8.2, 5 April 2017, to the DSMC Charter version 4.0, 2 August 2016, to the Data Management Plan version 2.0, 28 February 2017, to the Protocol Deviation Plan version 1.0 dated 26 September 2016 and the eCRF dated 17 March 2017.

1.2. Objectives of Statistical Analysis

This statistical analysis plan (SAP) is designed to outline the methods to be used in the SAD and MAD final analysis of study data in order to answer the study objective(s) of the entire study. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

The SAP is prepared in compliance with ICH E9.

2. STUDY DESIGN

2.1. Synopsis of Study Design

This is a randomized, double-blind (investigator and subject), placebo-controlled, single ascending and multiple ascending dose-escalation study to evaluate the safety, tolerability and pharmacokinetics and pharmacodynamics of QR-010 in subjects with CF who are homozygous for the ΔF508 mutation. Immunogenicity is to be evaluated amongst other safety considerations. Exploratory clinical efficacy measures are also included. There are two parts to the Phase 1b study: the study will start with four single ascending dose (SAD) cohorts and will move through four multiple ascending dose (MAD) cohorts.

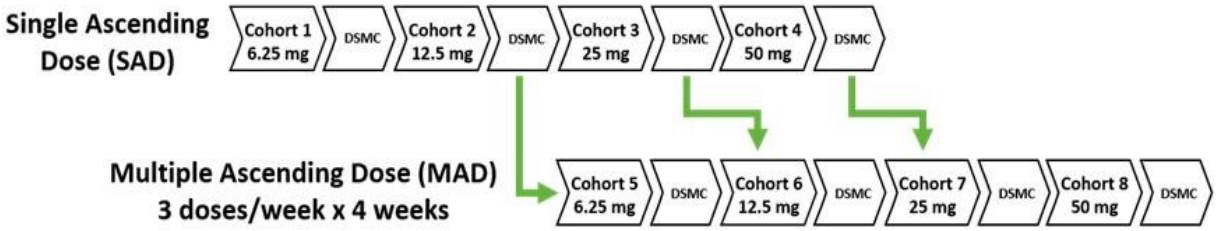
SAD (Cohorts 1-4): single dose inhaled administration. The doses for SAD cohorts are Placebo (0 mg), QR-010 6.25, 12.5, 25, or 50 mg. Subjects will receive the dose will be observed for a total 4 days, and will be discharged on Day 4. Subjects will return for PK and safety follow-up as an outpatient on Day 8.

MAD (Cohorts 5-8): multiple dose inhaled administration. The doses for the MAD cohorts are Placebo (0 mg), QR-010 6.25, 12.5, 25, or 50 mg, thrice weekly for 4 weeks, for a total of 12 doses per subject. Subjects are followed weekly with end of treatment (EoT) visit to be performed 7 days after last dose and a safety follow-up visit to be performed 28 days after last dose.

An independent Data Safety Monitoring Committee (DSMC) was designated to review all safety data at the end of each cohort and to determine the maximum tolerated dose (MTD).

A schematic of the study design is presented in Figure 1.

Figure 1: PQ-010-001 Study Schematic



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)

2.2. 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.

2.3. Determination of Maximum Tolerated Dose (MTD)

The MTD is defined as one dose level below the dose level at which 2 or more subjects receiving QR-010 experience a dose limiting toxicity (DLT) in the same organ class 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 2: 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)

2.4. Randomization Methodology

Within each dosing cohort, subjects will be randomized 3:1, QR-010 to placebo.

The randomization is performed using a centralized interactive web response system (IWRS).

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 pharmacist(s) 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.

2.5. Stopping Rules and Unblinding

2.5.1. Stopping Rules

At subject level: Subjects may withdraw from the study at any time without repercussion to their treatment or affiliation with their healthcare providers. Investigator can decide at any time during the study to discontinue treatment for an individual subject based on her/his own medical judgment. Reasons for stopping should be documented in the CRF (End of Treatment Visit), and subjects will be encouraged to participate to the follow-up period (End of Study Visit) for safety monitoring purposes.

At study level: 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. Refer to protocol and DSMC charter for description of the DLT/MTD criteria.

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 (i.e., at the MTD).

2.5.2. Unblinding

The DSMC is unblinded to the Study Treatment. Safety data from each cohort will be provided unblinded and evaluated by the DSMC at the end of each cohort, prior to escalation to the next dosing level. Additionally if AEs of interest occur at a Grade 2 level or higher, as defined in the protocol, they will be provided to the DSMC for evaluation in a timely fashion (i.e., without waiting for completion of the cohort) to support dose escalation decisions and determination of dose limiting toxicity events.

Sponsor personnel may be unblinded to subject treatments in order to permit 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.

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.

2.6. Study Procedures

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.

2.7. Efficacy, Pharmacokinetic, and Safety Variables

2.7.1. Efficacy Variables

Please refer to section 4.6

2.7.2. Pharmacokinetic Variables

Please refer to section 4.7

2.7.3. Safety Variables

Please refer to section 4.8

3. SUBJECT POPULATIONS

3.1. Population Definitions

The following subject populations will be evaluated and used for data presentation. Safety analyses will be conducted based on the safety population. Exploratory efficacy analyses will be conducted based on the Exploratory Analysis Population.

3.1.1. SAD

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

Safety Population: the population for safety analysis will consist of all subjects who receive any QR-010 or placebo.

Subjects will be analysed according to the actual treatment received (this is checked versus kit numbers, which may be different to randomization 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 analysed according to the actual treatment received. Applying this criterion is consistent with the objective of exploratory of clinical efficacy in this relatively small sample size phase 1 safety and tolerability study.

Pharmacokinetics (PK) Population: the population for PK analyses will consist of all subjects who receive at least one dose of QR-010 and who have sufficient drug concentrations to support analysis.

3.1.2. MAD

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 analysed according to the actual treatment received (this is checked versus kit numbers, which may be different to randomization 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 analysed according to the actual treatment received. Applying this criterion is consistent with the objective of exploratory of clinical efficacy in this relatively small sample size phase 1 safety and tolerability study.

Pharmacokinetics (PK) Population: the population for PK analyses will consist of all subjects who receive at least one dose of QR-010 and who have sufficient drug concentrations to support analysis. For subjects in whom dosing was discontinued early, pharmacokinetic parameters for week 4, dose 12 will not be generated, but all available PK concentrations in serum, urine and sputum will be listed regardless of time of last dose; however PK parameters will be generated on all other days where study dose was administered as per protocol.

3.2. Protocol Deviations

Protocol deviations are defined as a deviation from the approved protocol.

Prior to database lock, ProQR's Medical Monitor will review the study's protocol deviation list and will define/document which subjects/deviations are considered minor/major protocol deviations.

Protocol deviations will be summarized by characteristics (Minor/Major), category and reason. All protocol deviations will be presented in data listings.

4. STATISTICAL METHODS

4.1. Sample Size Justification

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 levels are to be expanded due to the occurrence of AEs of interest.

4.2. General Statistical Methods and Data Handling

4.2.1. Baseline Values

Unless otherwise specified, baseline data is defined as the data most recently collected prior to the first dose.

For Sweat Chloride, baseline is the average of all assessments of the day the closest to first dose, first dose day after dose time excluded.

4.2.2. Change (absolute) and % Change (relative change)

Change and % change (relative) from baseline is calculated as:

Change = Post baseline visit value – baseline value.

% Change = 100*((Post baseline visit value – baseline value)/baseline value).

If either the baseline or visit value is missing, the change from baseline/% change is set to "missing".

4.2.3. Study Day

Study Day is the number of days since the administration of the first dose of study drug, which is counted as Study Day 1. If the assessment date is after the date of the first dose, the study day is calculated as (date of assessment - date of the first dose administration + 1). If the assessment date is prior to the date of the first dose, the study day is calculated as (date of assessment - date of the first dose administration). All assessments prior to Study Day 1, including the Screening and Check-In visits, will have negative study days.

4.2.4. End of Study Date

End of study date is defined as the date when a subject completes the study (all doses given and all visits completed) or withdraws from the study early, it is computed as the maximum date for a subject-visit taken from any database panel.

4.2.5. Table Shell

Separate outputs will be produced for the SAD cohorts and the MAD cohorts. In general, the total group will be presented for disposition, baseline information, and treatment exposure, unless otherwise specified.

Table 3: Header for the SAD Cohort

	Placebo	QR-010 6.25 mg	QR-010 12.5 mg	QR-010 25 mg	QR-010 50 mg	Total SAD (optional)
Screened	…	…	…	…	…	…
Screen failure						
Treated						
Exploratory Analysis Population						
Safety Population						
Xxx						

Table 4: Header for the MAD Cohort

	Placebo	QR-010 6.25 mg	QR-010 12.5 mg	QR-010 25 mg	QR-010 50 mg	Total MAD (optional)
Screened	…	…	…	…	…	…
Screen failure						
Treated						
Exploratory Analysis Population						
Safety Population						
xxx						

4.2.6. Multiple Comparisons/Multiplicity

Due to the exploratory nature of the study, all tests for exploratory efficacy are conducted at alpha level 5%, two-sided (or 2.5% one-sided), and there will be no adjustment for multiplicity.

4.2.7. Visit Windows

4.2.7.1. General Rules

Definition of target visit dates for SAD:

Day 1 is defined as the date of first (and unique) dose. Day 2,3,4,8 are defined relatively to Day 1 (Ex: Day 4=Day 1+3).

Definition of target dose visits dates for MAD:

When possible, visits windows are defined with the doses dates.

- If a subject receives all 12 doses: target dates/times are the doses dates/times
- If a subject receives less than 12 doses: use the table below for definition of expected dates.
    - If there is a dose in the window EXPDATE +/-1 days then target visit date=this particular dose date.
    - If there is no dose in the window EXPDATE +/-1 days then the subject has missed the dose at the visit or missed the visit,
    - Then EXPDATE will be taken as the target visit date, with time 00:00.

Table 5: Target Visit/Days for MAD

Dose (Visit)	**Expected date EXPDATE** **(Dose n-1 date + expected number of days)**	**Target Dose Visit Date**
Dose 1 (Day 1)	Day 1	Dose 1 date
Dose 2 (Day 3)	Dose 1 date + 2 days (i.e. 3-1), time 00:00	• If any dose within expected date +/-1 days then = this dose date, • else = expected date (i.e. = Dose 1 date + 2 days)
Day 4	Day 3 Target date+1 day	Day 3 Target date+1 day
Dose 3 (Day 5)	Day 3 Target date + 2 days (5-3), time 00:00	• If any dose within expected date+/-1 days then = this dose date, • else = expected date (i.e. Day 3 Target Date + 2 days)
Dose 4 (Day 8)	Day 5 Target date + 3 days (8-5), time 00:00	"
Dose 5 (Day 10)	Day 8 Target date + 2 days, time 00:00	"
Dose 6 (Day 12)	Day 10 Target date + 2 days, time 00:00	"
Dose 7 (Day 15)	Day 12 Target date + 3 days, time 00:00	"
Dose 8 (Day 17)	Day 15 Target date + 2 days, time 00:00	"
Dose 9 (Day 19)	Day 17 Target date + 2 days, time 00:00	"
Dose 10 (Day 22)	Day 19 Target date + 3 days, time 00:00	"
Dose 11 (Day 24)	Day 22 Target date + 2 days, time 00:00	"
Dose 12 (Day 26)	Day 24 Target date + 2 days, time 00:00	"
Day 33	Day 26 Target date + 7 days	Day 26 Target date + 7
Day 54	Day 26 Target date + 28 days	Day 26 Target date + 28

For time points with time precision relative to dose (i.e. "Dose time+ XX min"), the time is computed with respect to the end time of dosing (end of inhalation).

4.2.7.2. Spirometry

Table 6: Time Point for Spirometry SAD

Time point	Target	Interval for Analysis
Baseline	Pre-dose Day 1	Most recent value prior to first dose
Day 1 10 min Post-dose	Day 1 dose end time+10 min	]Day 1 dose end time, Day 1 dose end time+20 min]
Day 1 30 min Post-dose	Day 1 dose end time+30 min	]Day 1 dose end time+20min, Day 1 dose end time+45 min]
Day 1 60 min Post-dose	Day 1 dose end time+60 min	]Day 1 dose end time+45min, Day 1 dose end time+90 min]
Day 1 2 hr Post-dose	Day 1 dose end time+2 hours	]Day 1 dose end time+90min, Day 1 dose end time+3h]
Day 1 4 hr Post-dose	Day 1 dose end time+4 hours	]Day 1 dose end time+3h, Day 1 dose end time+6h]
Day 1 8 hr Post-dose	Day 1 dose end time+8 hours	]Day 1 dose end time+6h, Day 2[
Day 2	Day 2	[Day 2, Day 4[
Day 4	Day 4	[Day 4, Day 7[
Day 8	Day 8	[Day 7, End of Study]

Table 7: Time point for Spirometry MAD

Time point	Target Date/Time	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 1 10 min Post-dose	Day 1 dose end time+10 min	]Day 1 dose end time, Day 1 dose end time +20min]
Day 1 30 min Post-dose	Day 1 dose end time+30 min	]Day 1 dose end time+20min, Day 1 dose end time +45min]
Day 1 60 min Post-dose	Day 1 dose end time+60 min	]Day 1 dose end time+45min, Day 1 dose end time +90min]
Day 1 2 hr Post-dose	Day 1 dose end time+2 hours	]Day 1 dose end time+90min, Day 1 dose end time +3h]
Day 1 4 hr Post-dose	Day 1 dose end time+4 hours	]Day 1 dose end time+3h, Day 1 dose end time +6h]
Day 1 8 hr Post-dose	Day 1 dose end time+8 hours	]Day 1 Dose end time+6h, Day 2[
Day 3 Pre-dose	Day 3 dose start time	[Day 2, Day 3 dose start time[
Day 3 20 min Post-dose	Day 3 dose end time +20 min	]Day 3 dose end time, Day 3 dose end time +40min]
Day 3 60 min Post-dose	Day 3 dose end time +60 min	]Day 3 dose end time+40min, Day 3 dose end time +2h]
Day 3 4 hr Post-dose	Day 3 dose end time+4 hours	]Day 3 dose end time+2h, Day 4[
Day 4	Day 4	]Day 3, Day 5[
Day 5 Pre-dose	Day 5 dose start time	[Day 5, Day 5 dose start time[
Day 5 20 min Post-dose	Day 5 dose end time +20 min	]Day 5 dose end time, Day 5 dose end time +40min]
Day 5 60 min Post-dose	Day 5 dose end time +60 min	]Day 5 dose end time+40min, Day 6]
Day 8 Pre-dose	Day 8 dose end time	[Day 7, Day 8 dose end time[
Day 8 20 min Post-dose	Day 8 dose end time +20 min	]Day 8 dose end time, Day 8 dose end time +40min]
Day 8 60 min Post-dose	Day 8 dose end time +60 min	]Day 8 dose end time+40min, Day 10]
Day 15 Pre-dose	Day 15 dose start time	]Day 10, Day 15 dose start time[
Day 15 20 min Post-dose	Day 15 dose end time +20 min	]Day 15 dose end time, Day 15 dose end time +40min]
Day 15 60 min Post-dose	Day 15 dose end time +60 min	]Day 15 dose end time+40min, Day 17]
Day 22 Pre-dose	Day 22 dose start time	]Day 17, Day 22 dose start time[
Day 22 20 min Post-dose	Day 22 dose end time +20 min	]Day 22 dose end time, Day 22 dose end time +40min]
Day 22 60 min Post-dose	Day 22 dose end time +60 min	]Day 22 dose end time+40min, Day 24]
Day 26 Pre-dose	Day 26 dose start time	]Day 24, Day 26 dose start time[
Day 26 20 min Post-dose	Day 26 dose end time +20 min	]Day 26 dose end time, Day 26 dose end time +40min]
Day 26 60 min Post-dose	Day 26 dose end time +60 min	]Day 26 dose end time+40min, Day 26 +3 days]

Day 33	Day 33	[Day 26+4 ; Day 33+7]
Day 54	Day 54	[Day 33+8 ; End of Study]

4.2.7.3. Laboratory Tests

Table 8: Time points for Hematology and Chemistry SAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 1 30 min Post-dose	Day 1 dose end time+30 min	]Day 1 dose end time, Day 1 dose end time +45 min]
Day 1 60 min Post-dose	Day 1 dose end time+60 min	]Day 1 dose end time+45min, Day 1 dose end time+90min]
Day 1 2 hr Post-dose	Day 1 dose end time+2 hours	]Day 1 dose end time+90min,Day 1 dose end time+3h]
Day 1 4 hr Post-dose	Day 1 dose end time+4 hours	]Day 1 dose end time+3h, Day 1 dose end time+6h]
Day 1 8 hr Post-dose	Day 1 dose end time+8 hours	]Day 1 dose end time+6h,Day 1 dose end time+10h]
Day 1 12 hr Post-dose	Day 1 dose end time+12 hours	]Day 1 dose end time+10h, Day 2[
Day 2	Day 2	[Day 2, Day 3[
Day 3	Day 3	[Day 3, Day 4[
Day 4	Day 4	[Day 4, Day 7[
Day 8	Day 8	[Day 7, End of study]

Table 9: Time points for Hematology and Chemistry MAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 1 30 min Post-dose	Day 1 dose end time+30 min	]Day 1 dose end time, Day 1 dose end time +45 min]
Day 1 60 min Post-dose	Day 1 dose end time+60 min	]Day 1 dose end time+45min, Day 1 dose end time+90min]
Day 1 2h Post-dose	Day 1 dose end time+2 hours	]Day 1 dose end time+90min,Day 1 dose end time+3h]
Day 1 4h Post-dose	Day 1 dose end time+4 hours	]Day 1 dose end time+3h, Day 1 dose end time+6h]
Day 1 8h Post-dose	Day 1 dose end time+8 hours	]Day 1 dose end time+6h, Day 1 dose end time+10h]
Day 1 12h Post-dose	Day 1 dose end time+12 hours	]Day 1 dose end time+10h, Day 3 dose end time]
Day 3 60min Post-dose	Day 3 dose end time+60min	]Day 3 dose end time, Day 3 dose end time+180min]
Day 3 4h Post-dose	Day 3 dose end time+4hours	]Day 3 dose end time+180min, Day 4[
Day 4	Day 4	[Day 4, Day 6]
Day 8 Pre-dose	Day 8 dose start time	[Day 7, Day 8 dose start time[
Day 8 15min Post-dose	Day 8 dose end time+15min	]Day 8 dose end time, Day 8 dose end time+30 min]
Day 8 60min Post-dose	Day 8 dose end time+60min	]Day 8 dose end time+30min, Day 8 dose end time+90min]
Day 8 2h Post-dose	Day 8 dose end time+2h	]Day 8 dose end time+90min, Day 10]
Day 15 Pre-dose	Day 15 dose start time	]Day 10, Day 15 dose start time[
Day 15 15min Post-dose	Day 15 dose end time+15min	]Day 15 dose end time, Day 15 dose end time+30 min]
Day 15 60min Post-dose	Day 15 dose end time+60min	]Day 15 dose end time+30min, Day 15 dose end time+90min]
Day 15 2h Post-dose	Day 15 dose end time+2h	]Day 15 dose end time+90min, Day 17]
Day 22 Pre-dose	Day 22 dose start time	]Day 17, Day 22 dose start time[
Day 22 15min Post-dose	Day 22 dose end time+15min	]Day 22 dose end time, Day 22 dose end time+30 min]
Day 22 60min Post-dose	Day 22 dose end time+60min	]Day 22 dose end time+30min, Day 22 dose end time+90min]
Day 22 2h Post-dose	Day 22 dose end time+2h	]Day 22 dose end time+90min, Day 26]
Day 33	Day 33	]Day 26 ; Day 33+7]
Day 54	Day 54	]Day 33+7 ; End of Study]

Table 10: Time points for Urinalysis SAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 2	Day 2	]Day 1 dose time, Day 3[
Day 3	Day 3	[Day 3, Day 4[
Day 4	Day 4	[Day 4, Day 7[
Day 8	Day 8	[Day 7, End of study]

Table 11: Time points for Urinalysis MAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 3 60min Post-dose	Day 3 dose end time+60min	]Day 1 dose end time, Day 3 dose end time+180min]
Day 3 4h Post-dose	Day 3 dose end time+4hours	]Day 3 dose end time+180min, Day 4[
Day 4	Day 4	[Day 4, Day 6]
Day 8 Pre-dose	Day 8 dose start time	[Day 7, Day 8 dose start time[
Day 8 60min Post-dose	Day 8 dose end time+60min	]Day 8 dose end time, Day 8 dose end time+90min]
Day 8 2h Post-dose	Day 8 dose end time+2h	]Day 8 dose end time+90min, Day 10]
Day 15 Pre-dose	Day 15 dose start time	]Day 10, Day 15 dose start time[
Day 15 60min Post-dose	Day 15 dose end time+60min	]Day 15 dose end time, Day 15 dose end time+90min]
Day 15 2h Post-dose	Day 15 dose end time+2h	]Day 15 dose end time+90min, Day 17]
Day 22 Pre-dose	Day 22 dose start time	]Day 17, Day 22 dose start time[
Day 22 60min Post-dose	Day 22 dose end time+60min	]Day 22 dose end time, Day 22 dose end time+90min]
Day 22 2h Post-dose	Day 22 dose end time+2h	]Day 22 dose end time+90min, Day 26]
Day 33	Day 33	]Day 26 ; Day 33+7]
Day 54	Day 54	]Day 33+7 ; End of Study]

Table 12: Time points for Coagulation, Direct Antiglobulin Test and Microbiology SAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 8	Day 8	]Day 1 dose end time, End of study]

Table 13: Time points for Coagulation MAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 8 Pre-dose	Day 8 dose start time	]Day 1 dose end time, Day 8 dose start time[
Day 33	Day 33	[Day 8 dose end time, End of Study]

Table 14: Time points for Direct Antiglobulin Test and Microbiology MAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 33	Day 33	]Day 1 dose end time, End of Study]

Table 15: Time points for CRP and ESR SAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 2	Day 2	[Day 2, Day 3[
Day 8	Day 8	[Day 3, End of Study]

Table 16: Time points for CRP and ESR MAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 15 Pre-dose	Day 15 dose start time	[Day 1 dose end time, Day 15 dose start time[
Day 22 Pre-dose	Day 22 dose start time	[Day 15 dose end time, Day 22 dose start time[
Day 33		[Day 22 dose end time, End of Study]

4.2.7.4. Sweat Chloride

Table 17: Time points for Sweat Chloride MAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 26	Day 26	[Day 1 dose end time, Day 26+3 days]
Day 33	Day 33	[Day 26+4 days ; Day 33+ 7 days]
Day 54	Day 54	[Day 33+8 days ; End of Study]

If several assessments are done on the same day, the average of these assessments will be used.

4.2.7.5. Vital Signs and Weight

Table 18: Time points for Vital Signs SAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 1 1min Post-dose	Day 1 dose end time+1min	]Day 1 dose end time, Day 1 dose end time+5min]
Day 1 10 min Post-dose	Day 1 dose end time+10min	]Day 1 dose end time+5min, Day 1 dose end time+20min]
Day 1 30min Post-dose	Day 1 dose end time+30min	]Day 1 dose end time+20min, Day 1 dose end time+45min]
Day 1 60min Post-dose	Day 1 dose end time+60min	]Day 1 dose end time+45min, Day 1 dose end time+90min]
Day 1 2hrs Post-dose	Day 1 dose end time+2h	]Day 1 dose end time+90min, Day 1 dose end time+3h]
Day 1 4hrs Post-dose	Day 1 dose end time+4h	]Day 1 dose end time+3h, Day 1 dose end time+8h]
Day 1 12hrs Post-dose	Day 1 dose end time+12h	]Day 1 dose end time+8h, Day 2[
Day 2	Day 2	[Day 2, Day 3[
Day 3	Day 3	[Day 3, Day 4[
Day 4	Day 4	[Day 4, Day 7[
Day 8	Day 8	[Day 7, End of Study]

Table 19: Time points for Weight SAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 8	Day 8	]Day 1 dose end time, End of study]

Table 20: Time points for Vital Signs MAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 1 1min Post-dose	Day 1 dose end time+1min	]Day 1 dose end time, Day 1 dose end time+5min]
Day 1 10 min Post-dose	Day 1 dose end time+10min	]Day 1 dose end time+5min, Day 1 dose end time+20min]
Day 1 30min Post-dose	Day 1 dose end time+30min	]Day 1 dose end time+20min, Day 1 dose end time+45min]
Day 1 60min Post-dose	Day 1 dose end time+60min	]Day 1 dose end time+45min, Day 1 dose end time+90min]
Day 1 2hrs Post-dose	Day 1 dose end time+2h	]Day 1 dose end time+90min, Day 1 dose end time+3h]
Day 1 4hrs Post-dose	Day 1 dose end time+4h	]Day 1 dose end time+3h, Day 1 dose end time+8h]
Day 1 12hrs Post-dose	Day 1 dose end time+12h	]Day 1 dose end time+8h, Day 3[
Day 3 Pre-dose	Day 3 dose start time	[Day 3, Day 3 dose start time[
Day 3 1min Post-dose	Day 3 dose end time+1min	]Day 3 dose end time, Day 3 dose end time+5min]
Day 3 10 min Post-dose	Day 3 dose end time+10min	]Day 3 dose end time+5min, Day 3 dose end time+20min]
Day 3 30min Post-dose	Day 3 dose end time+30min	]Day 3 dose end time+20min, Day 3 dose end time+45min]
Day 3 60min Post-dose	Day 3 dose end time+60min	]Day 3 dose end time+45min, Day 3 dose end time+90min]
Day 3 2hrs Post-dose	Day 3 dose end time+2h	]Day 3 dose end time+90min, Day 3 dose end time+3h]
Day 3 4hrs Post-dose	Day 3 dose end time+4h	]Day 3 dose end time+3h, Day 3 dose end time+8h]
Day 3 12hrs Post-dose	Day 3 dose end time+12h	]Day 3 dose end time+8h, Day 4[
Day 4	Day 4	[Day 4, Day 5[
Day 5 Pre-dose	Day 5 dose start time	[Day 5, Day 5 dose start time[
Day 5 1min Post-dose	Day 5 dose end time+1min	]Day 5 dose end time, Day 5 dose end time+5min]
Day 5 10 min Post-dose	Day 5 dose end time+10min	]Day 5 dose end time+5min, Day 5 dose end time+20min]
Day 5 30min Post-dose	Day 5 dose end time+30min	]Day 5 dose end time+20min, Day 5 dose end time+45min]
Day 5 60min Post-dose	Day 5 dose end time+60min	]Day 5 dose end time+45min, Day 5 dose end time+90min]
Day 5 2hrs Post-dose	Day 5 dose end time+2h	]Day 5 dose end time+90min, Day 7[
Day 8 Pre-dose	Day 8 dose start time	[Day 7, Day 8 dose start time[
Day 8 1min Post-dose	Day 8 dose end time+1min	]Day 8 dose end time, Day 8 dose end time+5min]
Day 8 10 min Post-dose	Day 8 dose end time+10min	]Day 8 dose end time+5min, Day 8 dose end time+20min]
Day 8 30min Post-dose	Day 8 dose end time+30min	]Day 8 dose end time+20min, Day 8 dose end time+45min]
Day 8 60min Post-dose	Day 8 dose end time+60min	]Day 8 dose end time+45min, Day 8 dose end time+90min]
Day 8 2hrs Post-dose	Day 8 dose end time+2h	]Day 8 dose end time+90min, Day 9[
Day 10 Pre-dose	Day 10 dose start time	[Day 9, Day 10 dose start time[

Day 12 Pre-dose	Day 12 dose start time	]Day 10 dose end time, Day 12 dose start time[
Day 15 Pre-dose	Day 15 dose start time	]Day 12 dose end time, Day 15 dose start time[
Day 15 1min Post-dose	Day 15 dose end time+1min	]Day 15 dose end time, Day 15 dose end time+5min]
Day 15 10 min Post-dose	Day 15 dose end time+10min	]Day 15 dose end time+5min, Day 15 dose end time+20min]
Day 15 30min Post-dose	Day 15 dose end time+30min	]Day 15 dose end time+20min, Day 15 dose end time+45min]
Day 15 60min Post-dose	Day 15 dose end time+60min	]Day 15 dose end time+45min, Day 15 dose end time+90min]
Day 15 2hrs Post-dose	Day 15 dose end time+2h	]Day 15 dose end time+90min, Day 16[
Day 17 Pre-dose	Day 17 dose start time	[Day 16, Day 17 dose start time[
Day 19 Pre-dose	Day 19 dose start time	]Day 17 dose end time, Day 19 dose start time[
Day 22 Pre-dose	Day 22 dose start time	]Day 19 dose end time, Day 22 dose start time[
Day 22 1min Post-dose	Day 22 dose end time+1min	]Day 22 dose end time, Day 22 dose end time+5min]
Day 22 10 min Post-dose	Day 22 dose end time+10min	]Day 22 dose end time+5min, Day 22 dose end time+20min]
Day 22 30min Post-dose	Day 22 dose end time+30min	]Day 22 dose end time+20min, Day 22 dose end time+45min]
Day 22 60min Post-dose	Day 22 dose end time+60min	]Day 22 dose end time+45min, Day 22 dose end time+90min]
Day 22 2hrs Post-dose	Day 22 dose end time+2h	]Day 22 dose end time+90min, Day 23 [
Day 24 Pre-dose	Day 24 dose start time	[Day 23, Day 24 dose start time[
Day 26 Pre-dose	Day 26 dose start time	]Day 24 dose end time, Day 26 dose start time[
Day 26 1min Post-dose	Day 26 dose end time+1min	]Day 26 dose end time, Day 26 dose end time+5min]
Day 26 10 min Post-dose	Day 26 dose end time+10min	]Day 26 dose end time+5min, Day 26 dose end time+20min]
Day 26 30min Post-dose	Day 26 dose end time+30min	]Day 26 dose end time+20min, Day 26 dose end time+45min]
Day 26 60min Post-dose	Day 26 dose end time+60min	]Day 26 dose end time+45min, Day 26 dose end time+90min]
Day 26 2hrs Post-dose	Day 26 dose end time+2h	]Day 26 dose end time+90min, Day 26+3days]
Day 33	Day 33	[Day 26+4 days ; Day 33+ 7 days]
Day 54	Day 54	[Day 33+8 days ; End of Study]

Table 21: Time points for Weight MAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 8	Day 8	]Day 1 dose end time, Day 8 + 3days]
Day 15	Day 15	[Day 8 +4days, Day 15+3 days]
Day 22	Day 22	[Day 15 +4days, Day 22+2 days]
Day 26	Day 26	[Day 22 +3days, Day 26+3 days]
Day 33	Day 33	[Day 26+4 days ; Day 33+ 7 days]
Day 54	Day 54	[Day 33+8 days ; End of Study]

4.2.7.6. Cystic Fibrosis Questionnaire Revised (CFQ-R)

Table 22: Time points for CFQ-R MAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 15	Day 15	[Day 1 dose end time, Day 15+9 days]
Day 33	Day 33	[Day 15+10 days ; Day 33+ 7 days]
Day 54	Day 54	[Day 33+8 days ; End of Study]

4.2.7.7. Electrocardiogram (ECG)

Table 23: Time points for ECG SAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 8	Day 8	]Day 1 dose end time, End of study]

Table 24: Time points for ECG MAD

Time point	Target	Interval for Analysis
Baseline	Day 1 dose start time	Most recent value prior to first dose
Day 33	Day 33	]Day 1 dose end time, End of Study]

4.2.8. Descriptive Statistics

Tabulations will be produced for appropriate demographic, baseline, efficacy, pharmacokinetic and safety parameters.

For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented.

For continuous variables, the mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum and maximum values will be presented.

For PK parameters percentage of coefficient of variation will be added.

4.2.9. Dictionaries

Adverse events and Medical history are to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) using the latest version available at the time of the lock for the SAD. The same version for the SAD and the MAD should be used.

Concomitant medications are to be coded using the WHODrug dictionary using the latest version available at the time of the lock.

4.2.10. Computing Environment

Statistical analyses will be performed using SAS statistical software (Version 9.2 or higher).

R software version 3.3.2 or higher will be also used for modelling and some graphics.

Cytel Proc MCPMod 1.1, East 6.3 PROCs for SAS will be used modelling

PK parameters will be generated using validated software (Phoenix WinNonlin® Version 6.3, or higher).

4.3. Interim Analyses

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

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

4.4. Subject Disposition

The number of subjects enrolled, number of screened failure will be tabulated.

The number of subjects in each population will be presented.

The number and percentage of subjects randomized, treated, completed treatment/discontinued from treatment (reasons), completed study and discontinued from the study and reasons will be presented for the safety population. The enrollment by geographic region (North America and Europe) region and by site will be tabulated.

Display will be presented by dose and total. Display may be repeated with the exploratory analysis population if exploratory analysis and safety populations differ.

A by-subject listing of study disposition (informed consent date, first dose, completion status, last treatment date, and last study date, including the reason for premature treatment/study withdrawal, if applicable) will be presented.

4.5. Demographic and Baseline Characteristics

Subject demographics including gender, ethnicity, race, age (years), baseline weight (kg), height (cm), and body mass index (BMI) (kg/m^2) will be tabulated. The baseline disease characteristics including pulmonary function (Forced Expiratory Volume in 1 second in Liters (FEV1 (L)), percent predicted FEV_1 (ppFEV1) (%), Sweat Chloride (mmol/L), and CFQ-RSS (only applicable in MAD cohort) will be summarized.

Data will be summarized by dose group and overall for subjects in the safety population. Display may be repeated with the exploratory analysis population if the exploratory analysis and safety populations differ.

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

BMI (kg/m^2) = Weight (kg) / [Height (m^2)]. BMI at each visit will be calculated using weight at the visit and height from the screening visit

ppFEV1 (%) = percent predicted FEV1 (with a unit of percentage points) is the ratio of FEV1 (L) to the predicted FEV1 (L), expressed as a percentage. The predicted FEV1 (L) is computed using the NHANES III normal value (REFERENCES

Hankinson et al., Spirometric Reference Values from a Sample of the General U.S. Population, (1999), AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, VOL 159 179-187) according to gender, race, age & height.

Demographic and Baseline data will be provided in data listings.

4.6. Medical History

Medical History will be summarized by dose group and overall for the safety population. Outputs may be repeated for the exploratory analysis population if exploratory analysis and safety populations differ.

4.7. Treatment Compliance and Extent of Treatment Exposure

Study drug will be administered in the clinic by qualified site personnel, by inhalation 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.

Treatment compliance and extent of exposure will be summarized by treatment group and overall, including time on study, number of study doses completed, number of subjects that completed dose at each dose visit, number of device pauses, status of full dose delivery, and nebulization duration at each dose visit. A listing of treatment exposure will be provided.

Treatment compliance will be presented for the safety population.

Outputs may be repeated for the exploratory analysis population if exploratory analysis and safety populations differ.

Time on study is defined as end of study date – first dose date +1. See section 4.2.4 for definition of end of study date.

For dose-visit dates, please refer to Section 4.2.7.

4.8. Exploratory Efficacy Evaluation

Efficacy analyses will be conducted using the exploratory analysis population.

4.8.1. SAD

The exploratory efficacy evaluations will include the following endpoints.

4.8.1.1. $ppFEV_1$ (%)

The $ppFEV_1$ value, absolute change from baseline and % change from baseline (relative change) will be presented descriptively over time (considering all time points from the visit windows for this parameter), per treatment group.

Graphical representation may be provided (mean change+ 95% CI overtime). Particularly a zoom on the data for the first 24 hours following first dose will be given).

In order to assess differences versus placebo a mixed model with repeated time measures on the change from baseline $ppFEV_1$ as outcome variable and including treatment, baseline $ppFEV_1$ value, time and interaction between time and treatment as covariates. By default, an unstructured covariance matrix will be used, unless convergence issue, in which case other covariance matrix will be explored. Adjusted means and corresponding confidence interval will be presented.

For Day 1, several spirometry assessments (pre and post dose) are planned. Subjects usually suffer from fatigue due to the multiple assessments, resulting in low post-dose values of FEV_1. Additionally, inhalation of the IMP may transiently impact the spirometry results. Thus the following time points will be included in the repeated measures analysis: Baseline, Day 2, Day 4 and Day 8, using the time windows.

Analyses to explore the dose response using the MCPMod methodology will be followed. A set of dose-response models will be tested including change from baseline $ppFEV_1$ at Day 4 as dependent variable, the treatment as factor (0, 6.25, 12.5, 25, 50 mg) and $ppFEV_1$ value at baseline (see Table 25 and Figure 2). The presence of a dose-response signal will be demonstrated if at least one of the candidate models is significant, adjusting for the different models (overall alpha=5% two-sided). Due to the small sample size, overall alpha for this exploratory dose-response analysis may be adapted. If a model is selected, an estimate of the minimum effective dose will be performed. Thresholds of 3%, 5% and 7% will be tested as sizes of interest of treatment effect (differences versus placebo).

Table 25: Set of Candidate Models for Dose-Response

Model	Parameters	
	ED 50	Scale δ
Linear	-	-
Loglinear	-	-
Emax	25	-
Exponential	-	12.5
Logistic	25	3

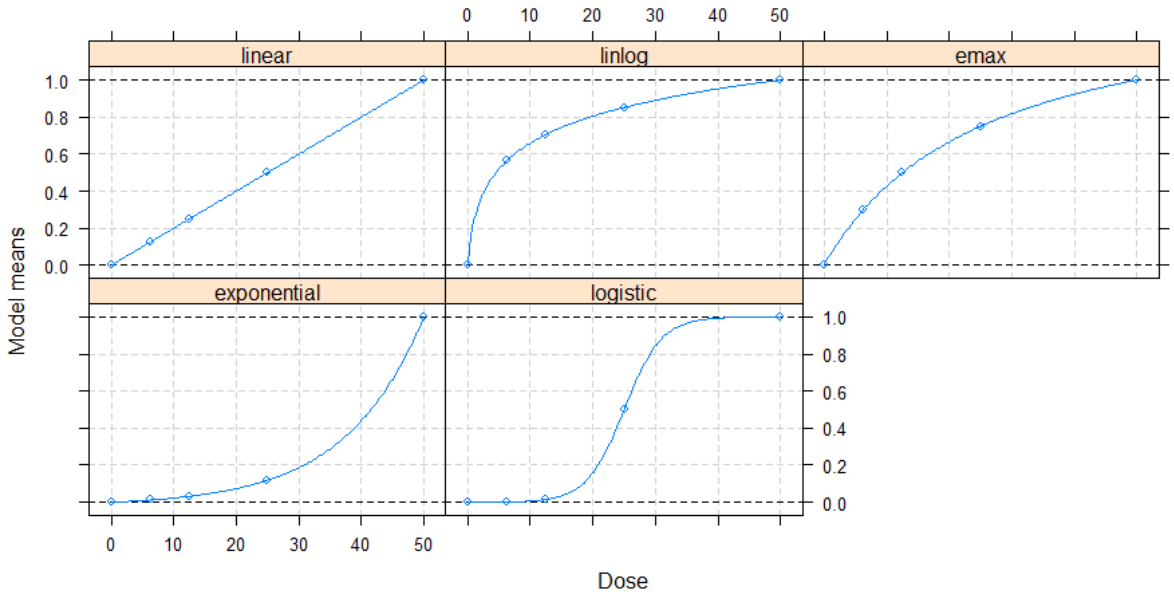


Figure 2: Candidate model for ppFEV1 dose response

4.8.1.2. FEV_1 (L)

FEV_1 value, change from baseline and % change from baseline will be presented descriptively over time, per treatment group. Graphical representation may be provided.

4.8.1.3. FVC (L)

FVC value, change from baseline and % change from baseline will be presented descriptively over time, per treatment group.

4.8.1.4. $FEF_{25/75}$ (L)

$FEF_{25/75}$ value, change from baseline and % change from baseline will be presented descriptively over time, per treatment group.

4.8.1.5. C-Reactive Protein (CRP) (mg/L)

CRP value and change from baseline will be presented descriptively over time, per treatment group. Graphical representation may be provided (mean +95% CI overtime).

4.8.1.6. Erythrocyte Sedimentation Rate (ESR) (mg/L)

ESR value and change from baseline will be presented descriptively over time, per treatment group. Graphical representation may be provided (mean +95% CI overtime).

4.8.2. MAD

4.8.2.1. $ppFEV_1$ (%)

The $ppFEV_1$ value, absolute change from baseline and % change from baseline (relative change) will be presented descriptively over time (considering all time points from the visit windows for this parameter), per treatment group.

Graphical representation may be provided (mean change+ 95% CI overtime). Particularly a zoom on the data for the first 24 hours following first dose will be given).

In addition, the SAD and MAD $ppFEV_1$ for the first 24 hours will be pooled in order to provide more robust data to the first day evolution.

The mixed-model analysis will be performed with repeated time measures on the change from baseline $ppFEV_1$ as outcome variable and including treatment, baseline $ppFEV_1$ value, time and interaction between time and treatment as covariates. By default, an unstructured covariance matrix will be used, unless convergence issue, in which case other covariance matrix will be explored. Adjusted means and corresponding confidence interval will be presented.

For visits with a dose, several spirometry assessments (pre and post dose) are planned. Subjects usually suffer from fatigue due to the multiple assessments, resulting in low post-dose values of FEV_1. Thus the following time points, concentrating on the pre-dose evaluations during treatment, and the post-treatment time points will be considered: Baseline, Day 3 pre-dose, Day 4, Day 5 pre-dose, Day 8 pre-dose, Day 15 pre-dose, Day 22 pre-dose, Day 26 pre-dose, Day 26 4 hours post-dose, Day 33 and Day 54. Differences versus Placebo will be estimated at Day 26 pre-dose, Day 26 4 hours post-dose, Day 33 and Day 54.

A sensitivity analysis including presence/absence of *Pseudomonas aeruginosa* at Baseline as a covariate will be performed.

Analyses to explore the dose response using the MCPMOD methodology as described in the SAD section will be followed. The change from baseline in $ppFEV_1$ at Day 26 pre-dose, Day 26 4 hours post-dose and Day 33 will be assessed.

4.8.2.2. FEV_1 (L)

FEV_1 value, change from baseline and % change from baseline will be presented descriptively over time, per treatment group.

4.8.2.3. FVC (L)

FVC value, change from baseline and % change from baseline will be presented descriptively over time, per treatment group.

4.8.2.4. $FEF_{25/75}$ (L)

$FEF_{25/75}$ value, change from baseline and % change from baseline will be presented descriptively over time, per treatment group.

4.8.2.5. Sweat Chloride (mmol/L)

Sweat chloride value and change from baseline will be presented descriptively over time, per treatment group. Graphical representation may be provided (mean change+ 95% CI overtime).

If several assessments are done on the same day, the average of these assessments will be used. See Section 4.2.1 for definition of baseline.

4.8.2.6. C-Reactive Protein (CRP) (mg/L)

CRP value and change from baseline will be presented descriptively over time, per treatment group.

Graphical representation will be provided (mean change from baseline +95% CI overtime).

4.8.2.7. Erythrocyte Sedimentation Rate (ESR) (mg/L)

ESR value and change from baseline will be presented descriptively over time, per treatment group.

Graphical representation will be provided (mean change from baseline+95% CI overtime).

4.8.2.8. Glucose

Glucose value and change from baseline will be presented descriptively over time, per treatment group.

A mixed model with repeated time measures on the change from baseline of glucose (mmol/L) as outcome variable and including treatment, baseline glucose value, time and interaction between time and treatment as covariates. By default, an unstructured covariance matrix will be used, unless convergence issue, in which case other covariance matrix will be explored. Adjusted means and corresponding confidence interval will be presented.

For some visits with a dose, several glucose assessments pre and/or post-dose are planned. We expect glucose values to differ post dose through the same day as meals are consumed; for stability of the data only the first glucose assessment performed at the selected visit days will be used.

Thus the following time points will be included in the repeated measures analysis: Baseline (baseline, Day 7 pre-dose, Day 15 pre-dose, Day 22 pre-dose, Day 33 and Day 54. Differences versus placebo will be estimated at Day 22, Day 33 and Day 54.

A sensitivity analysis including presence/absence of Cystic Fibrosis Related Diabetes with or without glucose intolerance at Baseline as a covariate will be performed.

Cystic Fibrosis related Diabetes at Baseline is defined as medical history term containing ‘diabetes’ ‘cystic fibrosis related diabetes’, ‘diabetes mellitus’. Glucose tolerance will be defined as medical history term containing ‘glucose tolerance impaired'. Descriptive statistics will be provided as appropriate.

The MCPMOD methodology will be applied to evaluate the dose-response, with change from baseline of glucose at Day 22 pre-dose as dependent variable. Thresholds of -0.5, -1, -2 will be tested as sizes of interest of treatment effect.

Graphical representation will be provided (mean change +95% CI overtime).

4.8.2.9. CFQ-R (Cystic Fibrosis Questionnaire – Revised)

The CFQ-R subject health-related quality of life questionnaire will be administered using the self-administered format (Adolescent and Adult version in the protocol Appendix 3), according

to the study schedule for MAD cohorts only. The CFQ-R is administered prior to any other test or procedure on each of the required study days (Baseline, Day 15, Day 33 and Day 54).

Cystic Fibrosis Questionnaire- Revised Respiratory Symptoms Score (CFQ-R RSS)

The CFQ-R RSS is calculated based on mean score of Questions 40 to 46 excluding question 43 as below if <=3 item scores are missing:

Assuming a coding of 1 to 4 with categories such as

1=A great deal / Always

2=Somewhat / Often

3=A little / Sometimes

4=Not at all / Never,

CFQ-R RSS = mean [(resp40, resp41, resp42, resp44, resp45, resp46)-1]/3*100;

The score will be missing if more than three of the six scores are missing.

Descriptive summary overtime will be provided for the values and change from baseline at each time point following the time windows, by treatment group.

A mixed model analysis with repeated time measures on the change from baseline of CFQ-R RSS as outcome variable, including treatment, baseline CFQ-R RSS value, time and interaction between time and treatment as covariates will be performed. By default, an unstructured covariance matrix will be used, unless convergence issue occurs, in which case other covariance matrix will be explored. Adjusted means and corresponding confidence interval will be presented. The following time points will be included in the repeated measures analysis: Baseline, Day 15, Day 33 and Day 54. Differences versus placebo will be estimated at Day 33 and Day 54.

A dose-response analysis using MCPMOD methodology will be performed with change from baseline of CFQ-R RSS at Day 33 as dependent variable, the treatment (0, 6.25, 12.5, 25, 50 mg) and CFQ-R RSS at baseline as factors. Thresholds of +4, +5, +8 and +10 will be tested as sizes of interest of treatment effect.

CFQ-R Other Domains:

Descriptive summary over time will be provided for the values and change from baseline at each time point following the time windows, by treatment group.

Details for re-coding are provided in http://www.psy.miami.edu/cfq_QLab/scoring.html .

All CFQ-R domain scores will be reported in listings.

4.8.2.10. Weight (kg)

Weight value and change from baseline will be presented descriptively over time at each time point (Baseline, Day 4, Day 15, Day 22, Day 26, Day 33, Day 54) per treatment group.

A mixed model with repeated time measures on the change from baseline of Weight as outcome variable, including treatment, baseline weight value, time and interaction between time and treatment as covariates will be performed. By default, an unstructured covariance matrix will be

used, unless convergence issue, in which case other covariance matrix will be explored. Adjusted means and corresponding confidence interval will be presented. The following time points will be included in the repeated measures analysis: Baseline, Day 15, Day 33 and Day 54. Differences versus placebo will be estimated at Day 33 and Day 54.

A dose-response analysis using MCPMOD methodology will be performed with change from baseline of weight at Day 33 as dependent variable, the treatment (0, 6.25, 12.5, 25, 50 mg) and weight at baseline as factors. Thresholds of 0.5, 1 , 2 and 3 (kg) will be tested as sizes of interest of treatment effect.

4.9. Pharmacokinetic Evaluations

In the SAD portion of the study, sample collections for support of PK analysis are planned as follows:

- Blood (i.e. serum): pre-dose (time 0), 0.5, 1, 2, 3, 4, 12, 24, 48, 54, 72, 168 hours post-dose.
- Urine: Pre-dose (time 0); Pooled from 0 to 4, 4 to 12, and 12 to 24 hours post-dose; and 48, 72, and 168 hours post dose.
- 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)

In the MAD portion of the study, sample collections for support of PK analysis are planned as follows:

Week 1, Dose 1

- Serum: 0, 0.5, 1, 2, 3, 4, 12; pre-Dose 2 (48 hours post-dose 1)
- Urine: Pre-dose; Pooled from 0 to 4 and 4 to 12 hours post Dose 1.
- Sputum: pre-dose, 3 samples obtained within first 6 hours post Dose 1.

Week 4, Dose 12

- Serum: pre-dose (0), 1, 2, 3, 4, 8, 24, 96, 144 (7 days post-last dose) and 648 hours (28 days post-last dose).
- Urine: Pre-dose; 24 and 96 hours, post-dose.

Additional sample collections are planned on interim study days during the MAD portion of the study. The measured concentrations will be presented in listings and used to confirm adequate QR-010 exposure; however, they will not be used to support generation of PK parameters. Additionally, urine concentrations that did not come from pooled collections or for which sample volumes were not collected will only be displayed in listings and will not be used to support generation of renal PK parameters.

The planned PK parameters for each portion of the study may be found in Table 26 below. Area under the serum concentration curve (AUC) will be generated using the linear-log trapezoidal rule.

Table 26: Planned Pharmacokinetic Parameters by Matrix and Study Day

Parameter	Definition	Calculation
SAD, Study Day 1, Serum PK Parameters		
Cmax	Maximum serum concentration	Observed
Tmax	Time of maximum serum concentration	Observed
AUClast	Area under the concentration-time curve from 0 to the last quantifiable serum concentration	Linear-Log trapezoidal method
AUCinf	Area under the concentration-time curve from 0 extrapolated to infinite	Calculated as AUC0-last + Cest,last/λz, where Cest,last is the estimated last measurable concentration
T1/2	Apparent terminal elimination half-life	ln(2)/λz, where λz is the apparent first-order terminal elimination rate constant.
λz	Terminal elimination rate constant	Log-linear regression of the concentration-time curve during terminal elimination
Cl/F	Apparent Clearance	Dose/AUCinf
Vd/F	Apparent volume of distribution	Dose/AUCinf* λz
SAD, Study Day 1, Urine PK Parameters		
Ae	Amount excreted unchanged in the urine	Cumulative: Sum of concentration* volume per collection interval
Fe%	Fraction of Dose excreted	Calculated as Ae/Dose, where Ae is the amount of unchanged drug excreted in urine during a collection

	unchanged in the urine	interval and D is the Dose
Clr	Renal Clearance	Calculated as Ae_{24}/AUC_{24} where Ae is the amount of unchanged drug excreted in urine during the first 24 hours post-dose and AUC_{24} is the Area under the concentration versus time curve from 0 to 24 hr.
MAD, Week 1, Dose 1, Serum		
Cmax	Maximum serum concentration	Observed
Tmax	Time of maximum serum concentration	Observed
AUCtau	Area under the concentration-time curve from 0 to the end of the dosing interval (tau, where tau will equal 48 hours).	Linear-log trapezoid
MAD, Week 4, Dose 12, Serum		
Ctrough	Trough serum concentration	Observed
Cmax	Maximum serum concentration	Observed
Tmax	Time of maximum serum concentration	Observed
AUCtau*	Area under the concentration-time curve from 0 to the end of the dosing interval (tau, where tau will equal 48 hours).	Linear-log trapezoid
Css	Steady-state concentration	AUCtau/tau, where tau will equal 48 hours

Ro	Accumulation ratio	AUCtau (week 4, dose 12)/ AUCtau (week 1, dose 1)
Ro,Cmax	Cmax, accumulation ratio	Cmax(week 4, dose 12)/ Cmax (week 1, dose 1)
Accumulation Index	Estimated accumulation index	$1/(1 - e^{-\lambda * tau})$
CL/F	Apparent clearance	Dose/AUCtau
V/F	Apparent volume	Dose/AUCtau* λz

*Sampling collection scheme during week 4, dose 12 allows for sample collection windows. The 96-hr sample time collection may occur between 48 and 144 hours post dose. For samples in which C_{48} was collected, AUCtau will be generated using observed data. For samples in which C_{48} was not collected, C_{48} will be estimated using each subject's individually estimated λ from week 4, dose 12, provided there is sufficient data to estimate the elimination rate constant. Data will be considered sufficient if there are no less than 3 time points included in the estimation, R-squared values are at least 0.9, and the percent of data extrapolated is less than 20%.

Concentrations below the limit of quantification (BQL) will be considered to be 0 concentration. With the possible exception of C_{48} (week 4, dose 12), missing values will not be imputed. If sufficient data are missing for a given subject, that subject may be considered non-evaluable for pharmacokinetic analysis and will not be included in the PK Population.

All serum, urine and sputum concentration data and the per-subject pharmacokinetic parameters will be displayed in listings. Summary statistics will be generated for each pharmacokinetic parameter unless there are less than three subjects will evaluable data. Summary statistics will include mean, median, geometric mean, standard deviation, minimum, maximum, and percentage of coefficient of variation. Concentration-time profiles will be plotted by individual and mean concentration-time profiles will be plotted by dose and study day on both the log and linear scales (if applicable). Dose-normalized parameters will be plotted for dose-ranging studies. Because there may be a relationship between pseudomonas and QR-010 systemic exposure, summary statistics and descriptive figures may also be generated by day, dose and pseudomona at the discretion of the team, but no formal statistical analysis will be performed and these additional tables and figures will be excluded from the top line report.

4.10. Safety Analyses

Safety analyses will be conducted using the safety population.

There will be separate reporting for SAD and MAD, with all treatment groups. No total column will be provided. In general, SOC and PT will be presented alphabetically.

4.10.1. Adverse Events

4.10.1.1. General Adverse Event Reporting

Adverse events will be summarized with MedDRA System Organ Class (SOC) and Preferred Term, by subject incidence rates, therefore, in any tabulation, a subject contributes only once to the count for a given adverse event (SOC or preferred term or AESI).

A treatment emergent Adverse Event (TEAE) is defined as an event with start date at/or after first dose.

An overall summary of TEAEs will include the number of

- Subjects with at least one TEAE,
- Number of TEAE,
- Subjects with study drug-related TEAEs,
- Subjects with device-related TEAEs,
- Subjects with TEAEs by maximum severity grade,
- Subjects with serious AEs,
- Subjects with TEAEs Leading to Treatment Discontinuation,
- Subjects with TEAEs Leading to Study Discontinuation,
- Deaths

The overall incidence of TEAEs will be summarized by treatment group and classified by SOC and PT. Reporting will include reports for Serious AEs, AEs leading to treatment discontinuation, deaths, AEs related to study drug, AEs related to device. AEs by SOC and PT will be presented by maximum severity.

An AE will be considered drug-related if the Investigator or Sponsor indicated that the event is coded “possibly” or "definitely" related to study drug or if the relationship is missing. The same definition applies for relationship to device.

AE intensity is graded on a 5 level category (Mild/Grade 1, Moderate/Grade 2, Severe/Grade 3, Life threatening/Grade 4, Death/Grade 5). Maximum intensity per PT is reported.

TEAEs will be listed in subject listings. Listings of Serious TEAEs, Death, Grade 2 or higher TEAEs will also be presented.

A listing for the non-treatment emergent events (with start date and time prior to first dose) will be provided, the listing will be provided only if events are collected.

4.10.1.2. AESI

AESI definition are based on MedDRA Coding version 17.1.

An overall summary of AESI and DLT will be presented. AESI will be summarized by SOC and PT and for AESI4, a summary of liver function test elevation will be presented. AESI will be reported in listings.

4.10.1.2.1. AESI1: Atelectasis

Atelectasis is defined as the AEs of at least Grade 2 with the preferred term that contains "atelectasis".

4.10.1.2.2. AESI2: Hypotension

Hypotension is defined as the AEs of at least Grade 2 with the preferred term that contains any of terms below:

- Blood pressure ambulatory decreased
- Blood pressure decreased
- Blood pressure diastolic decreased
- Blood pressure orthostatic decreased
- Blood pressure systolic decreased
- Diastolic hypotension
- Hypotension
- Mean arterial pressure decreased
- Orthostatic hypotension
- Procedural hypotension

4.10.1.2.3. AESI3: Bronchospasm

Bronchospasm is defined as the AEs of at least Grade 2 with the preferred term that contains “Bronchospasm" or "asthma" or "wheezing" or "bronchial obstruction"

4.10.1.2.4. AESI4: Liver Function Test Elevation

Liver Function Test Elevation is defined from laboratory data as: Alanine Aminotransferase (ALT) >3 x ULN or Aspartate Aminotransferase (AST) >3 x ULN and doubling from baseline value.

4.10.1.2.5. AESI5: Pneumonitis

Pneumonitis is defined as the AEs of at least Grade 2 with the preferred term that contains "pneumonitis ".

4.10.1.2.6. AESI6: Crackles

Crackles is defined as the AEs of at least Grade 2 with the preferred term that contains "crepitation" or "rales".

4.10.1.2.7. AESI7: Dypnoea

Dyspnoea is defined as the AEs of at least Grade 2 with the preferred term that contains "dyspnoea" or "orthopnoea".

4.10.1.2.8. AESI8: Hypoxia

Hypoxia is defined as: Pulse Oximeter < 88%

4.10.1.2.9. AESI9: Allergic Reaction

Allergic Reaction is defined as the AEs of at least Grade 2 with the preferred term that contains "Hypersensitivity" or "Alveolitis" or "vasculitis" or "urticaria" or "dermatitis allergic" or "anaphylactic" or "anaphylaxis".

4.10.1.3. DLT definition

Potential DLTs are reviewed and adjudicated by the DSMC. Adjudicated DLTs will be loaded from an excel file and summarized by treatment group. Individual subject listings will be provided for each DLT including severity.

4.10.1.4. Change FEV<=-15% from baseline

The number of subjects with a change from baseline of FEV_1 (L) <=-15% at least once and overtime will be summarized by treatment group. FEV_1 evolution will be graphically presented for those subjects. A listing will be provided.

4.10.2. Laboratory Data

Local laboratory measurements are performed for this study, thus different units and normal ranges may be collected. Summary statistics will be provided when relevant.

4.10.2.1. General Display

Laboratory measurements obtained will be summarized by treatment group overtime following analysis time points (time windows) that may differ according to parameter data collection.

Descriptive statistics for the continuous data of actual results and change from baseline for each time point will be presented. Frequencies and percentages per time point will be presented for categorical data.

Frequencies and percentages of subjects with values outside of the normal ranges overall (post-baseline) and for each time point will be presented.

Shift tables summarizing the count of subjects below, within and above the normal ranges at baseline and to maximum and to minimum value during treatment and after treatment for MAD and after treatment only for SAD will be presented. For shift tables all post-baseline assessments will be used (in particular unscheduled assessments).

Listing of laboratory data will be presented. A listing presenting the data for clinically relevant abnormal values will be provided.

4.10.2.2. Hematology

Hematology includes: hematocrit, hemoglobin, erythrocyte mean corpuscular HGB concentration, erythrocyte mean corpuscular hemoglobin, erythrocyte mean corpuscular volume, erythrocytes, white blood count, segmented neutrophils, bands, total neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count).

All analyses described in the general display section will be performed when possible.

4.10.2.3. Chemistry

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.

All analyses described in the general display section will be performed when possible.

4.10.2.4. Coagulation tests and Direct Antiglobulin Test

Coagulation tests include INR, PT, APTT, fibrinogen and total complement (CH50). All analyses described in the general display section will be performed when possible.

Direct Antiglobulin test results will be summarized over time and reported in listing. They will be included in Coagulation outputs.

4.10.2.5. Urinalysis

Urinalysis (by visual inspection and dipstick) will include color and appearance, microalbumin, casts, crystals, epithelial cells, erythrocytes, specific gravity, pH, protein, glucose, occult blood, ketones, bilirubin, leukocytes, leukocyte esterase, nitrite, and urobilinogen.

Urinalysis data will be reported in listings only.

4.10.2.6. Microbiology pathogen

Sputum sample or oropharyngeal swab for microbiology organism identification are collected prior to and after treatment. Number and frequency of observed pathogens (included details for others) will be provided by time point.

The following format will be displayed for (CRF defined categories and Others)

Table 27: Microbiology Pathogen List

Reported	Formatted	Flag for Pseudomonas
Terms from the coded list		
Achromobacter xylosoxidans		
Aspergillus spp		
Burkholderia spp		
Candida spp		
Hemophilus influenzae		

Inquilinus limosus		
Non-tuberculous mycobacterium - MAC		
Non-tuberculous mycobacterium - M.cheloni or M. abscessus		
Pandoraea apista		
Pseudomonas aeruginosa		Y
Ralstonia spp		
Staphylococcus aureus		
Stenotrophomonas maltophilia		
Terms from the Other category (free text)		
'commensal bacteria	Normal Flora	
BURKHOLDERIA CENOCEPACIA, STAFYLOCOCCUS AEREUS, YEAST	This is three different pathogens: Burkholderia spp, Staphylococcus aureus, Yeast spp * will be consider "Others", or in separate if the data changes.	
Escherichia coli	Escherichia coli	
MRSA	Staphylococcus aureus	
Methicillin Resistant Staph aureus	Staphylococcus aureus	
Methicillin-Resistant Staphylococcus	Staphylococcus aureus	
Mucoid Pseudomonas Aeruginosa	Pseudomonas aeruginosa	Y
Mycobacterium fortuitum	Mycobacterium fortuitum	
Normal Flora	Normal Flora	
PROTEUS MIRABILLIS	Proteus mirabilis	
Pseudomonas positive	Pseudomonas aeruginosa	Y
Yeast	Yeast spp	

enterobacter asburiae	Enterobacter spp	
enterobacter cloacae	Enterobacter spp	
fungi (non specific)	Fungi spp	
haemophylus parainfluenzae	Haemophilus parainfluenzae	
haemphilus influenza-candida albicans/dubliniencis	This is multiple pathogens: Haemophilus influenza, and Candida spp,	
micro organism filamentous fungus evoking	Fungi spp	
microbiota reasident	Normal flora	
microbiota resident	Normal flora	
mold	Mold spp	
proteus mirabilis	Proteus mirabilis	
staphylococcus aureus	Staphylococcus aureus	
yeast	Yeast spp	
yeasts	Yeast spp	

The list may be updated based on latest database.

4.10.2.7. Parameters collected at baseline only

Descriptive summaries of actual values will be reported for the following parameters: Tocopherol Vitamin E (continuous reporting) and Drug screen (categorical Negative/Positive).

4.10.2.8. Pregnancy test

Pregnancy test results will be presented in a by subject data listing.

4.10.3. Vital Signs and Oximetry

Descriptive summaries of actual values and changes from baseline of vital signs will be reported for each time point, in the following parameters: Height (baseline only), Weight, BMI, Heart rate, Systolic and Diastolic Blood Pressure, Temperature, Pulse rate and Pulse Oximetry.

By-subject listings of vital sign measurements will be presented including flag for abnormality (if exist). A special listing reporting vital signs measurements considered clinically relevant will be provided.

4.10.4. Physical Examinations

Physical examination abnormal findings will be presented in a by subject data listing.

4.10.5. Electrocardiogram

12-Lead Standard electrocardiogram data are collected as Normal/Abnormal. Number and percentage of Normal/Abnormal Not Clinically Significant/Abnormal Clinically Significant values will be presented overall (number of subjects) and by visit (prior to treatment and post treatment (Day 8 for SAD, Day 33 for MAD).

Clinically Significant Abnormal ECG results with comments will be reported in listings.

4.10.6. Prior and Concomitant Medications

Concomitant medications are to be coded using the WHO Drug dictionary.

Prior and Concomitant Medications will be tabulated separately by ATC level 2 and Preferred Name (number and percent of subjects). Tables will be sorted by alphabetical order of ATC level 2 and Preferred Name.

5. CHANGES TO PLANNED ANALYSES

As of this date, there have been no changes between the protocol-defined statistical analyses and pharmacokinetics analyses those presented in this statistical plan.

6. REFERENCES

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7. APPENDICES

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 Procedures	Screening	Check-In				Discharge				End of Study
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 Protocol Section 7.2 for details.

b See Protocol Section 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 FEV1, FVC, and FEF25-75.

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 Protocol 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 Protocol 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 Protocol 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 Protocol Section 7.2 for details.

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

[c] Includes FEV1, FVC, and FEF25-75.

[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 Protocol 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 Protocol 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 Protocol 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 Protocol 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 Protocol 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 Protocol 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 Protocol 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 Protocol 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 FEV1, FVC, and FEF25-75.
[d] See Protocol 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 Protocol 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 Protocol 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 Protocol 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 24 and 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 Protocol 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						
Urine microalbumin			X				
Urinalysis	X						
	Dose 4: Pre-dose, 60 minutes and 2 hours post dose Dose 10: Urine microalbumin pre-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				
Urinalysis	X				
	Dose 10: 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 Protocol Section 5.5.2 for details on these visits for subjects who withdraw prematurely from the study.

[b] Women of child-bearing potential only

[redacted]

Amendment to STATISTICAL ANALYSIS PLAN

Protocol PQ-010-001

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 Number: **(Version Date)**	PQ-010-001 Version 8.0, 04 April 2017, Version 8.1, 05 April 2017, Version 8.2, 05 April 2017
Name of Test Drug:	QR-010 Solution for Nebulization
Phase:	Phase 1b
Methodology:	Randomized, double-blind, 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)
Sponsor:	ProQR Therapeutics Zernikedreef 9 2333CK Leiden The Netherlands
Sponsor Representative:	[redacted] VP Clinical Development and Study Medical Monitor
Document Date:	13 October 2017
Document Version:	Amendment N°1 to SAP Version 1.0, 18 April 2017

SIGNATURE PAGE

Protocol Title:	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
Sponsor:	ProQR Therapeutics Zernikedreef 9 2333CK Leiden The Netherlands
Protocol Number:	PQ-010-001
Document Date/Version:	13 October 2017
[redacted] **Author:** [redacted] Biostatistician [redacted]	Signature [redacted] _____ Date: 13-Oct.-2017

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatory: [redacted] VP Clinical Development and Study Medical Monitor ProQR Therapeutics	Signature: [redacted] _____ Date: 16-Oct-2017
Sponsor Signatory: [redacted] VP Program Management ProQR Therapeutics	Signature: [redacted] _____ Date: 16-Oct-2017

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1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to document post hoc analysis requested to be undertaken for the 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, (PQ-010-001).

Reference is made to SAP V1.0, dated 18 April 2017.

2. SUBJECT POPULATIONS

2.1. Population Definitions (MAD)

Two new populations are introduced:

Per Protocol Population (MAD): The population for additional efficacy analyses consists of all subjects from the exploratory population that receive at least 10 out of 12 doses of QR-010 or placebo.

Subjects will be analyzed according to the actual treatment received.

Sensitivity Population for ppFEV1: This population consists of subjects from the Per Protocol Population, excluding outliers with a change from baseline in ppFEV1 >=20.

2.2. Subgroups Definitions

To explore the impact of the baseline status:

Subgroups of subjects with PPFEV1<90 and >=90% at baseline will be considered for PPFEV1 and CFQ-R RSS endpoints analyses.

Subgroups of subjects with CFQ-R RSS<75 and >=75 at baseline will be considered for CFQ-R RSS endpoints analyses.

The following subgroups of CFQ-R RSS at baseline by range of 10 points will also be considered for CFQ-R RSS analyses: .., [50;60[, [60;70[, [70;80[, [80;90[, [90;100].

3. ANALYSES

3.1. ppFEV1 (%)

Descriptive summaries will be performed on Per Protocol Populations and Sensitivity Population excluding outliers of PPFEV1. Summaries will repeated on subgroups of PPFEV1 at baseline for the 3 populations.

The mixed-model analysis described in the SAP will be repeated on the Per Protocol and Sensitivity Populations (using the following time points: Baseline, Day 4, Day 5 pre-dose, Day 8 pre-dose, Day 15 pre-dose, Day 22 pre-dose, Day 26 pre-dose, Day 26 4 hours post-dose, Day 33 and Day 54. Differences versus Placebo will be estimated at Day 15, Day 26 pre-dose, Day 26 4 hours post-dose, Day 33 and Day 54). Differences versus Placebo at Day 15 will also be assessed on Exploratory Population (in addition to planned time points).

The mixed model analysis will also be carried out on subgroups of PPFEV1 at baseline for the 3 populations. Due to the small sample size, the following time points only will be included in the model: Day 15 pre-dose, Day 26 pre-dose and Day 33.

The sensitivity analysis including presence/absence of *Pseudomonas aeruginosa* at Baseline as a covariate will be repeated on Per Protocol Populations. Day 15 will be added as time point of interest for both Exploratory and Per Protocol Populations.

Analyses to explore the dose response using the MCPMOD methodology as described in the SAP will be followed and repeated on Per Protocol Populations. The change from baseline in $ppFEV_1$ at Day 15 pre-dose (also on Exploratory Population), Day 26 pre-dose, Day 26 4 hours post-dose, Day 33 and Day 54 will be assessed.

In addition to the dose-responses shapes described in the SAP, a quadratic model with umbrella-shape will be tested. Parameters of the dose-responses shapes models may be adapted to fit the data.

3.2. CFQ-R (Cystic Fibrosis Questionnaire – Revised) RSS

Descriptive summaries will be repeated on Per Protocol Populations. Summaries will be repeated on subgroups of PPFEV1 at baseline (<90;>=90) and CFQ-R RSS at baseline (<75;>=75 and subgroups by 10 points).

The mixed model analysis on CFQ-R RSS score described in the SAP will be repeated on Per Protocol Populations. Differences versus placebo will be estimated at Day 15, Day 33 and Day 54.

The mixed model analysis will be performed on subgroups of PPFEV1 at baseline (>90;>=90) and CFQ-R RSS at baseline (<75; >=75) for the 2 populations.

Dose-response analyses using MCPMOD methodology will be repeated on the Per Protocol Population. Thresholds of +4, +5, +8 and +10 +12 will be tested as sizes of interest of treatment effect.

In addition to the dose-responses shapes described in the SAP, a quadratic model with umbrella-shape will be tested. Parameters of the dose-responses shapes models may be adapted to fit the data.

3.3. Correlation between PPFEV1 and CFQ-R RSS

The relationship between PPFEV1 and CFQ-R RSS will be assessed with Pearson correlations and scatterplots with regression lines for:

- Baseline: Actual values, overall
- Day 33: Actual values and changes from baseline, by treatment group
- Day 26 pre-dose for PPFEV1 and Day 33 for CFQ-R RSS: Actual values and changes from baseline, by treatment group

3.4. Weight (kg) and Sweat Chloride (mmol/L)

Analyses for Weight and Sweat Chloride will be repeated on Per Protocol Populations.