CLINICAL STUDY PROTOCOL COVER PAGE

A PHASE 1B/2A, MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, SINGLE AND MULTIPLE ASCENDING DOSE STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF AP-PA02 MULTI-PHAGE THERAPEUTIC CANDIDATE FOR INHALATION IN SUBJECTS WITH CYSTIC FIBROSIS AND CHRONIC PULMONARY *PSEUDOMONAS AERUGINOSA* (*PA*) INFECTION

Protocol No.	AP-PA02-101
Protocol/Amendment Date:	13 August 2021
Protocol Version:	6.0
Supersedes:	Version 5.0
IND Number	IND21780
Sponsor:	Armata Pharmaceuticals, Inc.
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INVESTIGATOR SIGNATURE PAGE

Armata Pharmaceuticals, Inc.

Protocol No. AP-PA02-101

Version No. 6.0
13 August 2021

PRINCIPAL INVESTIGATOR COMMITMENT:

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

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

_____

Printed Name of Principal Investigator

_____

Signature of Principal Investigator

_____

Date

_____

Institution

_____

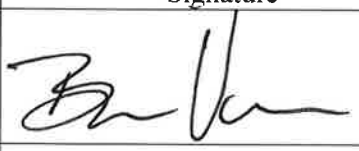
Address of Institution

PROTOCOL APPROVAL PAGE

A Phase 1b/2a, Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety and Tolerability of AP-PA02 Multi-Phage Therapeutic Candidate for Inhalation in Subjects with Cystic Fibrosis and Chronic Pulmonary *Pseudomonas aeruginosa* (*Pa*) Infection

Sponsor:	Armata Pharmaceuticals, Inc.
Protocol No.	AP-PA02-101
Protocol/Amendment Date:	13 August 2021
Protocol Version:	6.0

The undersigned have reviewed the format and content of this protocol and have approved its issuance.

Name and Title	Signature	Date Signed
Brian Varnum, PhD President and Chief Development Officer Armata Pharmaceuticals, Inc.		13 Aug 2021
Dr. Mina Pastagia, MD Vice President, Clinical Development Armata Pharmaceuticals, Inc.	Mina Pastagia	13Aug2021
Vicki White Sr. Director, Clinical Operations Armata Pharmaceuticals, Inc.	Vicki M White	13 Aug 2021

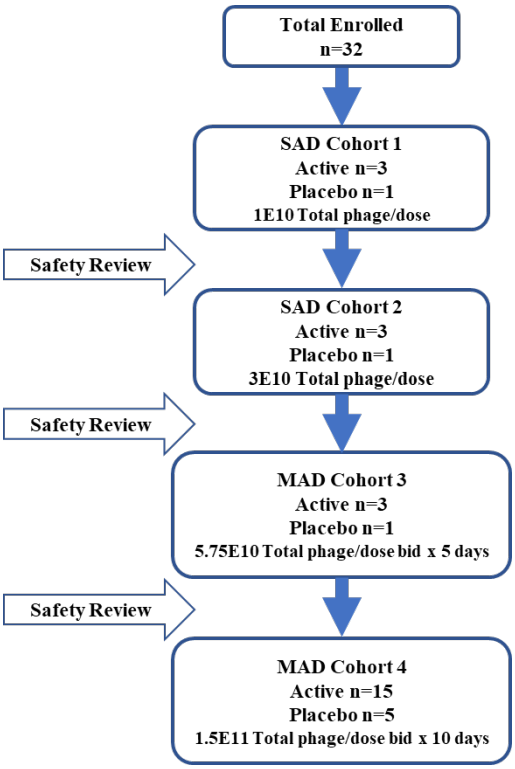
STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), the Declaration of Helsinki, and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 SYNOPSIS

Name of Sponsor/Company:	Armata Pharmaceuticals, Inc.
Name of Investigational Product:	AP-PA02
Protocol Number:	**AP-PA02-101**
Title of Study:	A Phase 1b/2a, Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety and Tolerability of AP-PA02 Multi-Phage Therapeutic Candidate for Inhalation in Subjects with Cystic Fibrosis and Chronic Pulmonary *Pseudomonas aeruginosa* (*Pa*) Infection
Investigators:	To be determined
Study Centers:	Approximately 30 centers in the United States
Phase of Development:	1b/2a
Duration of Subject Participation:	Part 1 Single-Ascending Dose (SAD) Cohorts 1-2: Subjects are on study for a total of 29 Days Part 2 Multiple-Ascending Dose (MAD) Cohorts 3-4: Subjects are on study for a total of approximately 33 days for Cohort 3, and approximately 38 days for Cohort 4
Number of Subjects (planned):	Total of approximately 32 subjects 8 subjects in Part 1 SAD Cohorts: Two dose cohorts, 4 subjects per dose cohort (randomized 3:1, AP-PA02 vs. placebo) 24 subjects in Part 2 MAD Cohorts: Two dose cohorts, 4 subjects in Cohort 3, and 20 subjects in Cohort 4 (randomized 3:1, AP-PA02 vs. placebo)
Objectives:	***Part 1: Single Ascending Dose (SAD) Evaluation*** Primary: Evaluate the safety and tolerability of a single dose of AP-PA02 administered via inhalation. Exploratory: Examine phage distribution and clearance, evidence of clinical efficacy, and the impact of phage therapy on the bacterial target after a single dose of AP-PA02 administered via inhalation. ***Part 2: Multiple Ascending Dose (MAD) Evaluation*** Primary:

	Evaluate the safety and tolerability of multiple doses of AP-PA02 administered via inhalation. Secondary: Explore *P. aeruginosa* recovery in sputum following multiple doses of AP PA02 administered via inhalation. Exploratory: Examine phage distribution and clearance, evidence of clinical efficacy, and the impact of phage therapy on the bacterial target following multiple doses of AP-PA02 administered via inhalation.
Study Design:	This is a Phase 1b/2a, double-blind, randomized, placebo-controlled, single and multiple ascending dose study to evaluate the safety, tolerability and phage recovery profile of AP-PA02 administered by inhalation. Figure 1: Cohort Progression Schematic  Figure 2: Enrollment by Cohort Schematic 

	Part 1: Single Ascending Dose Evaluation Part 1 will evaluate single doses of AP-PA02 administered by inhalation in medically stable cystic fibrosis patients with chronic pulmonary *P. aeruginosa* infection at time of Screening. A total of 8 subjects, 4 subjects in each of 2 sequential dose cohorts, will be randomized to receive either AP-PA02 or placebo administered via inhalation at the clinical site. Each cohort of 4 patients will be randomized with 3 subjects to receive active treatment and 1 subject to receive placebo. Eligible subjects will be randomized to receive a single dose of AP-PA02 (or placebo), administered on Day 1. Subjects will be followed for safety for approximately 4 weeks post-dose. The first two subjects of the same dose cohort will not be permitted to dose on the same day to allow for adequate safety monitoring between subjects. Following dosing, subjects will be closely monitored for safety, including repeated measurements of vital signs (blood pressure, heart rate, respiratory rate and body temperature) and SpO_2 (at 10, 30 and 60 minutes, and 2, 4 and 7 hours post dose), 12-lead ECG (at 60 minutes post dose) and spirometry (at 30 minutes, 60 minutes and 7 hours post dose), and vitals, SpO_2 and spirometry are repeated at 24 and 48 hours post dose as outlined in Appendix 1 Schedule of Assessments. *Part 1 SAD Cohort Safety Monitoring:* Following the completion of each SAD dose cohort, a Safety Monitoring Committee (SMC) will review all available safety data through Day 8. Initiation of dosing for the next cohort will be determined by the SMC based on an adequate safety profile demonstrated in the prior cohort. If subjects experience any acute AEs post-dose administration (regardless of causal relationship to study drug) that have not resolved by the time the subject is to be discharged home on Day 1, it will be left up to the discretion of the Investigator to admit the subject overnight for continued observation, if in the best interest of the subject. All patients will be followed for 29 days for safety and phage recovery profile, or until resolution of study drug or study-related AEs. If AEs of interest occur at a Grade 3 level or higher in two or more subjects in a cohort, then an additional 4 subjects (3 active, 1 placebo) may be added to the cohort.

	Part 2: Multiple Ascending Dose (MAD) Evaluation: The MAD portion of the study will also be double-blinded, randomized, placebo-controlled, to evaluate the safety and efficacy of two dose levels of AP-PA02. The first MAD cohort (Cohort 3) will enroll 4 subjects, where 3 subjects will be randomized to active treatment and 1 subject randomized to receive placebo. The second MAD cohort (Cohort 4) will enroll 20 subjects, where 15 subjects will be randomized to receive active treatment, and 5 subjects will be randomized to receive placebo. The total number of placebo patients will be 6 subjects across the two dose cohorts. For subjects on a usual regimen of inhaled antipseudomonal antibiotics, Day 1 will need to be scheduled relative to the subject's inhaled antibiotic(s) cycle. Subjects will be followed for safety for approximately 4 weeks post-last dose. Once enrolled, each subject in Cohorts 3 and 4 will receive one fractionated dose of AP-PA02 or placebo (one dose distributed over two administrations in the same day), for five or ten consecutive days in the clinic, respectively. Following each dose, subjects will be closely monitored for safety, including repeated measurements of vital signs (blood pressure, heart rate, respiratory rate and body temperature) and SpO_2, 12-lead ECG (at 60 minutes post first dose) and spirometry, as outlined in Appendix 1 Schedule of Assessments. For Cohort 3, subjects will return to the clinic approximately 24 hours post-last dose for safety evaluations and phage titer sampling, for Visits 6 through 8, and End of Study Visit. For Cohort 4, subjects will return to the clinic approximately 24 hours post-last dose for safety evaluations and phage titer sampling, and on Visits 11 through 13, and End of Study Visit. Additional follow-up visits for safety and anti-drug antibody (ADA) titer will be performed at approximately 14 days post-last dose and at the End of Study Visit. Follow-up 12-lead ECG will also be performed at the End of Study Visit. The first two randomized subjects of each MAD dose cohort will not be permitted to initiate dosing (Day 1) on the same day, to allow for adequate safety review. *Part 2 MAD Cohort Safety Monitoring:* Initiation of enrollment into Part 2 of this study will be dependent on the positive recommendation and concurrence of the Sponsor following the SMC safety review following Cohort 2, per Figures 1 and 2 above. Following the completion of dosing of MAD cohort 3, the SMC will review all available safety data through Visit 7 (including any additional safety data from the SAD cohorts collected to date), before enrollment can continue into Cohort 4.

	If subjects experience any acute AEs post-dose administration (regardless of causal relationship to study drug) that have not resolved by the time the subject is to be discharged home on a given dosing day, it will be left up to the discretion of the Investigator to admit the subject overnight for continued observation, if in the best interest of the subject, and subsequent doses may be delayed or held, with concurrence from Study Medical Monitor and/or Sponsor designee. All patients will be followed through End of Study Visit for safety and efficacy, or until resolution or stabilization of study drug or study-related AEs.
Diagnosis and Main Criteria for Eligibility:	Patients who meet the following inclusion criteria and none of the exclusion criteria will be considered eligible for enrollment in the study.
Inclusion Criteria:	1. Able and willing to comply with the protocol and provide written consent prior to any study-specific procedures. 2. Male or female ≥ 18 years old. 3. Body mass index (BMI) of ≥ 18 kg/m^2 4. Must have documentation of one of the following criteria: a. Sweat chloride ≥ 60 mEq/L by quantitative pilocarpine iontophoresis test performed at or prior to Screening -OR- b. Known disease-causing mutations in the CFTR gene on each chromosome. 5. Clinically stable with no significant changes in health status within the 7 days prior to and including the Screening Visit 6. Evidence of chronic pulmonary *Pa* infection. Evidence includes one or more of the following: a. Microbiological evidence of pulmonary *Pa* infection within the last 24 months b. Current utilization of chronic-suppressive inhaled antibiotics for *Pa* c. Oral or parenteral anti-pseudomonal therapy administered within the last 2 years 7. Willing to undergo sputum induction procedures at Screening, Baseline and at designated time points during the study, and willing to provide expectorated sputum samples at all other timepoints (for subjects who are able to expectorate). 8. Must have ≥10^4 CFU of *Pa* per gram of induced sputum obtained at Screening 9. Subject's *Pa* isolates are susceptible to AP-PA02, based on morphotypes obtained from induced sputum obtained at Screening.

	10. For SAD: $FEV_1 \geq 60\%$ of predicted normal for age, gender, race and height [using Global Lung Function Initiative (GLI) standards] at Screening (regardless of the timing of the most recent prior administration of short-acting bronchodilator). For MAD: $FEV_1 \geq 40\%$ of predicted normal for age, gender, race and height [using Global Lung Function Initiative (GLI) standards] at Screening (regardless of the timing of the most recent prior administration of short-acting bronchodilator). 11. Stable lung function, determined by the Investigator, provided that the FEV_1 at the Baseline Visit has not decreased by more than 5% compared to the FEV_1 measured at Screening. 12. Able to reproducibly perform pulmonary function tests (spirometry) per ATS/ERS Standards. 13. For subjects to be enrolled into Part 1 of the protocol (SAD), dosing relative to their inhaled antibiotics schedule is not restricted; subjects participating in Part 1 SAD may schedule Day 1 at any time. For subjects to be enrolled into Part 2 of the protocol (MAD), if on inhaled antibiotics for chronic suppression of *P. aeruginosa:* a. Subjects on a single, chronically-administered inhaled antipseudomonal antibiotic, with no interruption of therapy or on two or more alternating inhaled antipseudomonal antibiotics, must remain on the same regimen from Screening through the end of the study. Day 1 can be scheduled at any time. b. Subjects on a chronically-administered routine of an intermittent inhaled antipseudomonal antibiotic (one month "on", one month "off") must be at least 6 days and not more than 17 days into the on- or off-month on Day 1. c. Subjects on a chronically-administered routine of inhaled antipseudomonal antibiotic, not following a monthly on/off inhaled antibiotic schedule may be enrolled provided the subject is on the on-cycle of the inhaled antibiotic from the Baseline Visit through approximately 14 days after the last study drug dose. d. Subjects not on chronically-administered inhaled antipseudomonal antibiotics may be scheduled for Day 1 at any time. 14. Creatinine clearance > 80 mL/min, as calculated by Cockcroft-Gault equation based on actual body weight 15. Ability to comply with study visits and study procedures as judged by the investigator 16. Female subjects of childbearing potential must agree to use a highly effective method of birth control (defined as those, alone or in combination, that result in a low failure rate [i.e. less than

	1% per year]) from Day 1 through 60 days following the last dose of study drug 17. Male subjects must agree to use barrier contraception (i.e. condoms) from Day 1 through 60 days following the last dose of study drug 18. The following criteria relate to acceptable laboratory values at Screening. a. Hemoglobin > 8 g/dL b. WBC < 14,000/μL c. Platelet count > 150 x 10^3/μL d. Prothrombin time (PT), International Normalized Ratio (INR) and partial thromboplastin time (PTT) within normal limits. Subjects with values outside the normal range may be permitted if the value is not clinically significant in the opinion of the Investigator, with concurrence from the Study Medical Monitor and/or Sponsor designee.
Exclusion Criteria:	1. Decrease in body weight within 90 days prior to Screening that is considered clinically significant by the Investigator 2. Abnormal vital signs at Screening: heart rate (hr) > 110 beats per minute (bpm) at rest; systolic blood pressure > 160 or < 90 mmHg; respiration rate > 24 breaths per minute; and SpO_2 < 92% at rest on room air 3. Subject history of, or patient-reported family history of, prolonged QT syndrome; or a QTc interval > 450 msec (males) or > 470 msec (females) using Fridericia's formula (QTcF) 4. Use of supplemental oxygen during the day at rest 5. Serum albumin < 2.5g/dL at Screening 6. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values greater than 3X the upper limit of normal (ULN) at Screening. 7. Oral or parenteral antibiotics received within 30 days prior to the Baseline Visit for acute pulmonary exacerbation. Inhaled antibiotic use for chronic suppression of *P. aeruginosa* is acceptable. 8. Any infection as determined to be clinically significant in the opinion of the Investigator with concurrence from the Sponsor's Medical Monitor and/or designee that results in receiving new systemic antimicrobial therapy within 30 days prior to the Baseline Visit. 9. Currently receiving anti-pseudomonal antibiotic treatment for acute sinusitis. 10. Currently receiving systemic corticosteroids at a dose greater than the equivalent of 10 mg/day of prednisone

	11. Currently receiving treatment for active infection with nontuberculous mycobacteria (NTM), *Staphylococcus aureus,* or *Burkholderia cepacia* complex lung infection. 12. Currently receiving treatment for aspergillosis or ABPA (allergic bronchopulmonary aspergillosis). 13. Subject initiated on a CFTR potentiator/corrector therapy, such as Trikafta®, less than 90 days prior to Screening. 14. Acquired or primary immunodeficiency syndromes 15. Active pulmonary malignancy (primary or metastatic) or any malignancy requiring chemotherapy or radiation therapy within one year prior to screening or anticipated during the study period 16. History of lung transplantation 17. Hemoptysis of greater than 30 mLs (cumulative) within 90 days prior to Day 1 or hospitalization for hemoptysis within 6 months of Day 1 18. Female pregnant or breastfeeding 19. Use of any investigational device or administration of any investigational products within 8 weeks or five therapeutic half-lives prior to study Day 1, whichever is longer. 20. Smoking more than 10 cigarettes or 2 cigars or 2 pipes per day, or nicotine equivalent from vaping, from within 3 months prior to screening through the end of the study. 21. Presence or medical history of clinically significant condition which precludes study participation or prevents determination of outcome measures. 22. Any severe, acute, or chronic medical or psychiatric condition, laboratory abnormality, or condition other than CF that, in the opinion of the Investigator, participation in the study is not in the best interest of the patient, puts the subject at undue risk, interferes with the results of the study, or makes the subject otherwise unsuitable for study participation. 23. Prior participation in study AP-PA02-101. Subjects previously enrolled in this study and received at least one dose of study drug are ineligible for re-enrollment.
Test Product, Dosage and Mode of Administration:	AP-PA02 is a proprietary multi-phage therapeutic candidate. Each of the bacteriophage drug products (DPs) comprising AP-PA02 will be supplied in glass vials as a sterile, single-use (non-preserved) solution, to be combined at the clinical site prior to administration to the subject. AP-PA02 will be administered in the clinic using PARI eflow® investigational electronic nebulizer. The SAD cohorts will test a combination of 3 bacteriophage DPs, and the MAD cohorts will test a combination of 5 bacteriophage DPs. The AP-PA02 dose administered to each subject will be determined based on cohort assignment. Dosage (in estimated plaque-forming units, or PFUs) per cohort shown below.

<table>
<tr><td></td><td>
<table>
<tr><th>Cohort</th><th>Each Dose (estimated PFUs)</th><th>Total Daily Dose (estimated PFUs)</th><th>Total Dose Per Treatment Course (estimated PFUs)</th></tr>
<tr><td>1 (single dose)</td><td>1E10</td><td></td><td></td></tr>
<tr><td>2 (single dose)</td><td>3E10</td><td></td><td></td></tr>
<tr><td>3 (BID x 5 days)</td><td>5.75E10</td><td>1.15E11</td><td>5.75E11</td></tr>
<tr><td>4 (BID x 10 days)</td><td>1.5E11</td><td>3E11</td><td>3E12</td></tr>
</table>
</td></tr>
<tr><td>Duration of Treatment:</td><td>SAD cohorts 1 and 2: One day.
MAD cohorts 3 and 4:
Cohort 3: Two fractionated doses administered on five consecutive days
Cohort 4: Two fractionated doses administered on ten consecutive days</td></tr>
<tr><td>Reference Therapy, Dosage and Mode of Administration:</td><td>Placebo is dilution buffer, comprised of 132 mM NaCl, 1 mM $CaCl_2$ dihydrate, 10 mM $MgCl_2$ hexahydrate, 10 mM Tris Base, sterile water for injection solution with pH 7.4 adjusted with HCl, supplied in glass vials.
Placebo will be administered in the clinic using PARI eflow® investigational electronic nebulizer.</td></tr>
<tr><td>Criteria for Evaluation:</td><td></td></tr>
<tr><td>Safety and Tolerability:</td><td>Safety will be assessed by monitoring AEs, vital signs, laboratory data (chemistries, hematology and urinalysis), immunogenicity evaluation, electrocardiograms (ECGs), pulmonary function, and physical examinations.</td></tr>
<tr><td>Phage Recovery:</td><td>Phage recovery of AP-PA02 will be based on AP-PA02 levels as measured in sputum and venous blood samples at time points specified in the Schedule of Procedures.</td></tr>
<tr><td>Efficacy:</td><td>Sputum Pa density as measured in sputum samples at time points specified in the Schedule of Procedures.</td></tr>
<tr><td>Exploratory:</td><td>The following will be performed or collected for exploratory evaluation and analysis:
• Determine anti-pseudomonas antibiotic sensitivity of Pa isolates at specified time points during the study
• Change from baseline of in vitro sensitivity of subject Pa isolates to AP-PA02 and/or individual phage components
• Cystic Fibrosis Questionnaire-Revised Respiratory Symptom Scale score (CFQ-R RSS)</td></tr>
</table>

	• Cystic Fibrosis Respiratory Symptom Diary (CFRSD) and Chronic Respiratory Infection Symptom Score (CRISS)
Statistical Methods:	Descriptive statistics will be calculated for all endpoints.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition/Explanation
ABPA	allergic bronchopulmonary aspergillosis
ADA	anti-drug antibody
ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS/ERS	American Thoracic Society / European Respiratory Society
AUC	Area Under the Curve
$AUC_{0-\infty}$	Area under the curve from time zero to infinity
AUC_{0-t}	Area under the curve from time zero to the final time point (last quantifiable sample)
$AUC_{0-\tau}$	Area under the curve within a dosing interval at Steady-State
AUC_{last}	Area under the plasma concentration-time curve from. time zero to time of last measurable concentration
BID	Twice a day
BMI	body mass index
bpm	beats per minute; breaths per minute
BUN	blood urea nitrogen
C	Celsius
$C_{avg, ss}$	Average Concentration at Steady-State
C_{last}	Last Observed Concentration
C_{max}	Maximum Concentration
$C_{max, ss}$	Maximum Concentration at Steady-State
$C_{min, ss}$	Minimum Concentration at Steady-State
CBC	complete blood count
CF	cystic fibrosis
CFR	Code of Federal Regulations
CFQ-R	Cystic Fibrosis Questionnaire-Revised

Abbreviation or Term	Definition/Explanation
CFRSD	Cystic Fibrosis Respiratory Symptom Diary
CFU	colony-forming units
CL/F	Apparent Clearance
Clinically significant	An abnormal finding/laboratory value that indicates a new disease process, an exacerbation or worsening of an existing condition, or requires further action(s) to be taken (e.g. initiation of new therapy).
CRF, eCRF	case report form, electronic case report form
CRISS	Chronic Respiratory Infection Symptom Score
CRO	Contract Research Organization
CSR	Clinical Study Report
dL	Deciliter
DLT	Dose–Limiting Toxicity
DP	Drug Product
DS	Drug Substance
EC, IEC	Ethics Committee, Independent Ethics Committee
ECG	electrocardiogram
eFlow	The Investigational eFlow® Nebulizer System (PARI Respiratory Equipment)
FDA	Food and Drug Administration
FEF_{25-75}	Forced Expiratory Flow between 25 and 75% of the FVC
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
g	Gram
GCP	Good Clinical Practice
GLI	Global Lung Function Initiative
HHS	Health and Human Services
HR	heart rate
ICH	International Conference on Harmonisation
IND	Investigational New Drug

Abbreviation or Term	Definition/Explanation
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	Intravenous
kg	Kilogram
L	Liter
LABA	long-acting inhaled β-agonist
LEC	Local Ethics Committee
LLQ	lower limit of quantification
LPS	lipopolysaccharide
MAD	Multiple Ascending Dose
µg	Microgram
µL	Microliter
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalent
mg	Milligram
mL	Milliliter
mmHg	millimeters of mercury
mmol	Millimole
MOI	multiplicity of infection
Pa, P. aeruginosa	*Pseudomonas aeruginosa*
PFU	plaque-forming unit
PT	prothrombin time, preferred term
PTT	partial thromboplastin time
qs	quantity sufficient
QTc	corrected QT interval

Abbreviation or Term	Definition/Explanation
QTcF	corrected QT interval using Fredericia's formula
RR	respiratory rate
SABA	short-acting inhaled β-agonist
SAD	Single Ascending Dose
SAP	Statistical Analysis Plan
SAE	serious adverse event
SMC	Safety Monitoring Committee
SOC	system organ class, standard of care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{½}$	terminal half-life
TEAE	treatment-emergent adverse event
TLF	tables, listings and figures
T_{max}	Time to maximum concentration (C_{max})
$T_{max, ss}$	Time to maximum concentration (C_{max}) at Study-State
ULN	upper limit of normal
US	United States

2 INTRODUCTION

Armata Pharmaceuticals, Inc. (Armata, the Sponsor) is developing a proprietary multi-phage therapeutic candidate (AP-PA02) for the treatment of *Pseudomonas aeruginosa* pulmonary infections. The intended route of clinical administration is oral inhalation (inhalation) of aerosolized AP-PA02.

2.1 Cystic Fibrosis

Cystic fibrosis (CF) is a genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CF affects over 30,000 people in the United States (US) (approximately 70,000 worldwide) with approximately 1,000 new diagnoses per year (Cystic Fibrosis Foundation Patient Registry 2018). Dysfunction of the CFTR gene leads to dysfunction in multiple organs (Mall and Hartl 2014), but particularly the lungs, where a failure of hydration of airway secretions results in thick mucus, chronic inflammation, airway remodeling, and recurrent infections (Pettit and Fellner 2014). Lung function continues to decline over time, punctuated by pulmonary exacerbations with increased cough, shortness of breath, and infections that result in rapid declines in lung function (Parkins et al. 2012). For these reasons, CF remains the most common fatal hereditary lung disease (Mall and Hartl 2014).

2.2 Chronic *Pa* Lower Respiratory Tract Infection is a Major Cause of Morbidity and Mortality in CF

Outcomes for people with CF have improved significantly in recent years through early screening (Smyth et al. 2014), the development and use of CFTR modulators (Pettit and Fellner 2014), and other therapies. Treatment of pulmonary *Pa* infections using inhaled antibiotics is an especially important part of CF disease modulation. Chronic *Pa* infections in CF are associated with worsening lung function, frequent pulmonary exacerbations, and increased mortality (Courtney et al. 2007; Kerem et al. 2014; Taccetti et al. 2005). In chronic lower respiratory tract *Pa* infections, the goal of antibiotic therapy is suppression, and a majority of patients are on a regimen of either continuous alternating therapy or regular intermittent therapy with 28-day cycles of inhaled tobramycin, aztreonam, and/or colistin (Nichols et al. 2019) consistent with current guidelines (Smyth et al. 2014; Mogayzel et al. 2013). With routine use of inhaled antibiotics, many patients with chronic *Pa* infection have improved lung function and less frequent exacerbations (Ramsey et al. 1993; Conway 1999; Sawicki et al. 2012; Mayer-Hamblett et al. 2015). However, numerous CF patients still experience clinical deterioration despite routine inhaled antibiotics (Nichols et al. 2019), hence the need for more effective therapies, ideally with a different mechanism of action compared to traditional antibiotics, for the treatment of **chronic** *Pa* infection. This first-in-human clinical trial will study the safety, tolerability, and efficacy of inhaled AP-PA02 phage therapy in subjects with CF and chronic *Pa* infection.

2.3 Phage as Antimicrobials

Lytic phages are viruses that specifically infect and kill bacteria. There are estimated to be more than 10^{31} bacteriophages (ten million trillion trillion) on Earth. They can be found

wherever bacteria exist, such as soil and seawater, extreme environments, wastewater, hospitals, and animal and human tissues (Clokie et al. 2011). Phages are completely devoid of metabolic activity and depend on bacterial translation machinery to multiply, and have no affinity for eukaryotic cells.

Phages have a number of potential advantages over traditional chemical antibiotics. Phages infect both antibiotic-sensitive and -resistant bacteria, and therefore the antimicrobial activity of phages is completely independent of antibiotic resistance (Bragg et al. 2014; Chan et al. 2018; Schooley et al. 2017; Dedrick et al. 2019). The primary advantage of phage activity is their extreme specificity towards a bacterial species; this aspect of phage biology suggests that fewer adverse effects on the gut microbiome will be seen with phage therapy compared with traditional antibiotics, which affect many bacterial species (Dissanayake et al. 2019; Cieplak et al. 2018; Denou et al. 2009). Phages also have *in vitro* efficacy against biofilms, where antibiotics are poorly effective (Parasion et al. 2014). Finally, the so-called traits of "self-dosing"— amplification at the site of bacterial infection - and "self-limiting" - failure to amplify and clearance of phage once bacteria are eliminated - are seen as another significant advantage of phage use as antimicrobials.

The clinical potential of virulent bacteriophage as antibacterial agents was first recognized by Felix d'Herelle, one of the pioneers of the phage therapy field, in the early 1900's (d'Herelle 1931; Twort 1936). Phages were discovered in 1915 at the Pasteur Institute and were shown to kill bacteria taken from patients suffering from dysentery. Throughout the pre-antibiotic era, phages were widely used as a therapeutic agent to combat a variety of bacterial infections (Twort 1936). However, phage use was displaced by the common use of broad-spectrum antibiotics in the early 1940s, particularly in Western medicine (Kortright et al. 2019). The recent development of multi-drug resistant bacterial infections has led to reconsideration of alternative antimicrobial therapies such as phage.

Phage therapy has been widely used in human medicine for the past century up through present day (Kutateladze and Adamia 2010). However, the safety and effectiveness of these therapies have not been conclusively established due to the lack of randomized, controlled clinical studies.

2.3.1 Mechanism of Action

Phages initiate infection by recognizing a specific receptor on the surface of their target bacterium, a process known as adsorption (Bertozzi et al. 2016; Barbu et al. 2016) (Figure 1). Once bound to its receptor, the phage initiates genome translocation to the cytoplasm, and bacterial metabolism is quickly subverted and channeled towards phage replication and production of virions (Weigel and Seitz 2006).

Phage infection culminates with lysis of the infected cell and release of progeny (Young 2014). Lysis is triggered by the controlled opening of holes in the cellular membrane releasing cell-wall degrading enzymes commonly referred to as lysins (Cahill and Young 2019). These lysins have intrinsic antimicrobial activities (Van Tassell et al. 2016; Abdelkader et al. 2019). While cell lysis is obviously bactericidal, phages possess multiple functions, such as preventing the capacity to divide or maintain a normal metabolism, that

also effectively kill cells (Bouet et al. 1996). When there are no target bacteria left for the phages to infect, they are removed through the body's natural clearance processes.

Figure 1 Lytic Cycle of Bacteriophages

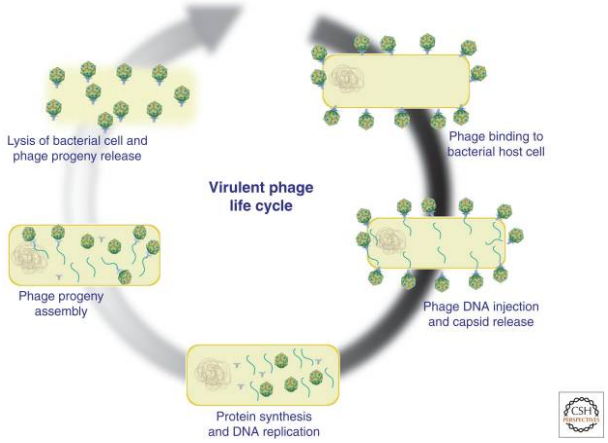


Figure 1. Schematic representation of virulent phage infection, replication and lysis of bacterial host cells (Barbu et al., 2016).

2.3.2 Clinical Candidate AP-PA02

AP-PA02 is a proprietary multi-phage therapeutic candidate aimed at treating *P. aeruginosa* infections. The initial formulation (tested in single dose Cohorts 1 and 2) will be comprised of three active, lytic *P. aeruginosa* bacteriophages: ARPA0003, ARPA0022, and ARPA0034. The formulation to be tested in multiple dose cohorts 3 and 4 will be comprised of the same three bacteriophages as was tested in Cohorts 1 and 2, and will also include two additional, lytic *P. aeruginosa* bacteriophages: ARPA0002 and ARPA0028. Table 1 summarizes the molecular characteristics of each bacteriophage.

Table 1 Molecular Characteristics of the Individual Bacteriophages in AP-PA02

Phage	Family	Genus	Genome Structure	Genome Size (kb)	No. of Encoded Proteins	Manufacturing Host	Host Receptor
Initial 3-phage formulation							
ARPA0003	Myoviridae	Pbunavirus	dsDNA	64	97	PAK (WH-SGI-V-07193)	LPS
ARPA0022	Myoviridae	Pbunavirus	dsDNA	67	99	PAO1 ΔalgD (GH-SGI-V-07209)	LPS
ARPA0034	Podoviridae	Phikmvvirus	dsDNA	44	55	PAO1 ΔalgC (GH-SGI-V-07210)	Pili
Phages added for 5-phage formulation							
ARPA0002	Myoviridae	Pakpunavirus	dsDNA	94	198	PAK ΔalgD (GH-AR-17604)	LPS
ARPA0028	Myoviridae	Bruynoghevirus	dsDNA	45	71	DCF47	LPS

Abbreviations: LPS = Lipopolysaccharide; dsDNA: double-stranded DNA (deoxyribonucleic acid)

Each bacteriophage was isolated from the environment by enrichment on strains of *P. aeruginosa*, amplified by fermentation in vegetable broth on its manufacturing host, and purified through multiple processes including tangential-flow-filtration and anion-exchange chromatography. The purification processes are robust with good yields resulting in phage drug substances (DS) with a high degree of purity as assessed by determination of levels of endotoxins, host-cell DNA, and host-cell proteins, each well below target specifications.

The DPs that comprise AP-PA02 and the placebo are manufactured and released under cGMP conditions by Armata Pharmaceuticals, Inc. The intended route of clinical administration is oral inhalation of nebulized AP-PA02.

Refer to Section 3 for additional product information.

2.4 Background

2.4.1 Pharmacology

The pharmacological rationale for AP-PA02 is based on a comprehensive series of *in vitro* and *in vivo* studies which demonstrate the antimicrobial potential of the phage drug candidate. The initial version of AP-PA02 (three-phage product consisting of ARPA0034, ARPA0003, and ARPA0022) has desirable characteristics such as potency of individual phage, breadth of clinical isolate coverage by individual phages and by the three-phage product. Adding two new phages, ARPA0002 and ARPA0028, increases the number of clinical isolates sensitive to AP-PA02 and the number of isolates sensitive to at least two phages. Using plate-based plaquing and liquid assays detailing the killing kinetics of *Pa*, AP-PA02 with five phages has activity against the majority of clinical *Pa* isolates, infecting

nearly 91% of tested strains, which equates to an 11% increase in susceptibility over the 3-phage cocktail. Additionally, approximately 80% of isolates are infected by two or more of the five phages representing a 17% increase over the three-phage product, theoretically improving product potency, and offsetting the potential for the development of resistance.

AP-PA02 selectivity for *Pa* has been demonstrated by a lack of activity against a panel of other organisms, as would be expected for bacteriophage biology. *In vitro* testing also displays activity of AP-PA02 against *Pa* biofilms. Collectively, the antimicrobial activity data illustrate that AP-PA02 is a potent and selective therapeutic candidate against clinical CF isolates.

To assure potential activity is not impaired in the target physiological compartments post-dosing, AP-PA02 activity was confirmed in relevant biological fluids, namely sputum and plasma. Additionally, AP-PA02 does not interfere with current standard-of-care antibiotics including tobramycin, aztreonam, colistin, and additional therapies including hypertonic saline and the beta agonist Salbutamol. For several CF clinical isolates, synergy between AP-PA02 and either tobramycin or aztreonam was observed.

The potential for the bacteriophage particle to stimulate the immune system through direct activation of innate immunity mechanisms or through enhanced stimulation by lysed bacterial components was evaluated *in vitro* with primary human peripheral blood monocytes (PBMCs). No direct stimulation was observed with phage alone, and no increase in pro-inflammatory cytokines is detected when phage and bacteria are co-cultured with PBMCs. The lack of an inflammatory response to AP-PA02 drug product *in vitro* confirms high drug purity and demonstrates the rapid lysis event of *Pa* by AP-PA02 does not stimulate the immune system above that seen with whole bacteria.

The pharmacokinetics of AP-PA02 were evaluated *in vivo* to assess the stability, activity and distribution of phage. Intranasal administration of AP-AP02 to mice resulted in persistent phage concentrations in the lungs with minimal systemic and off target exposure. These are desired qualities for a therapeutic to treat *P. aeruginosa* lung infections and supports the rationale of inhalation therapy in humans. Murine models of *Pa* lung infection were established to evaluate the antimicrobial potential of the three-phage product in the lung compartment. Models of *Pa* lung infections show efficacy and provide data to model human doses. Efficacy was observed with bacteriophage doses that reach a multiplicity of infection (MOI) above 1, with robust protection in the survival model when the MOI of infection of phage to the *Pa* inoculum is approximately 10 or greater. These results guide the phase 1 dose selections which align with published compassionate use cases.

Anti-Drug Antibody Assay

In considering future patient populations and treatment paradigms, another important consideration is the potential for the development of ADA against AP-PA02, which could impact tolerability or efficacy. This study will also assess ADA development across the treated population.

A bridge ELISA has been developed for detection of human (ADA) against each of the three phages in the product utilized for Cohorts 1 and 2 that meets the sensitivity requirements by the Food and Drug Administration (FDA) of at least 100 ng/mL. Using purified antibodies specific to each phage to bridge two phage particles together, this assay can be used to detect ADAs in human serum at a range of 2-7300 ng/mL. This assay will be utilized to detect ADA response in blood samples collected from subjects enrolled into this clinical trial. These data will be useful in determining whether ADAs occur after a single dose. Antibodies to the additional two phages in the five-phage product to be used in Cohorts 3 and 4 have been generated and a bridge ELISA is currently being developed. This will help determine whether ADAs are produced following multiple doses, for 5 or 10 days. Assessments will be made of titer, isotype, whether the ADAs are neutralizing, and these data will guide future concepts of effective treatment regimens.

2.4.2 Clinical Experience

No prior clinical studies have been conducted with AP-PA02.

2.4.3 Armata's Experience with Phage Therapy for Pseudomonas aeruginosa

The first generation of an anti-*Pa* phage therapeutic product AP-PA01 was administered under compassionate use to treat patients with serious or life-threatening *Pa* lung infections associated with lung transplantation, cystic fibrosis, or ventilator-associated pneumonia and empyema have been treated with inhaled or intravenous (IV) routes of administration. One of these cases was recently featured in the peer-reviewed journal *Infection* after IV AP-PA01 was administered acutely to treat a cystic fibrosis patient who had developed a multidrug-resistant bacterial *Pa* infection (Law et al. 2019). Maddocks et al described the treatment of a 77 year old woman with *Pa* ventilator-associated pneumonia and empyema with both inhaled and IV administration of AP-PA01 in the *American Journal of Respiratory and Critical Care Medicine* (Maddocks et al. 2019).

Human exposure through compassionate use of AP-PA01 has been helpful in demonstrating the promise of phage therapy, however, no conclusions regarding applicable safety and tolerability cannot be drawn from the experience with AP-PA01. Leveraging our experiences with AP-PA01, AP-PA02 is a new therapeutic candidate composed of five phages representing multiple phage families that demonstrates improved clinical isolate coverage over AP-PA01. AP-PA02 is the clinical product that will be tested in the first-in-human clinical trial described in this protocol to study the safety, tolerability, and efficacy of phage therapy in subjects with CF and chronic airway *Pa* infection.

2.5 Study Rationale

2.5.1 Clinical Development Strategy

In this clinical study, the safety and tolerability of AP-PA02 in adults with chronic airway *Pa* infection will be assessed in a single ascending dose/multiple ascending dose SAD/MAD clinical trial. This study will provide an initial understanding of the safety profile of inhaled AP-PA02 to treat chronic pulmonary *Pa* infection in subjects with CF. This study will also

yield information on the persistence of AP-PA02 in the airway and on the systemic exposure following inhalation. These data will help guide dosing regimens for future studies. Potential efficacy of AP-PA02 will be assessed through measures of *Pa* bacterial sputum density, FEV_1 and patient-reported outcomes. Though not powered for efficacy endpoints, these measures, especially *Pa* sputum density, will also inform dose and schedule for future trials.

A key hallmark of phage therapy with replication-competent natural phage is the potential for an auto-regulated dose that is characterized by propagation of phage until sensitive organisms are eliminated. Because of this feature, the proposed dosing in the SAD/MAD is a first step towards defining an acute treatment regimen that accomplishes decolonization. Thus, phage therapy is envisioned to be an intermittent therapy and not chronic suppressive therapy. Given that chronic suppressive antipseudomonal antibiotic therapy is the standard of care (SOC), dosing of AP-PA02 will be in addition to SOC. The dose levels and schedule of dose in this study are designed to test the hypothesis that sufficient, acute exposure of AP-PA02 can result in productive bacteriophage infection and functional eradication of *Pa*.

In addition to antibiotic SOC, use of CFTR modulator therapy is increasingly common and has led to significant improvements in lung function, sweat chloride, numbers of pulmonary exacerbations, body mass index, and quality of life for people with CF (Pettit and Fellner, 2014). While ivacaftor produced rapid decreases in sputum *Pa* density that were sustained for up to a year, sputum *Pa* density rebounded (Hisert et al, 2017). Therefore, additional antimicrobial therapies for patients with chronic pulmonary *Pa* infection are still needed, even in this new era of widespread use of CFTR modulator therapies.

The study design is modeled after a conservative, traditional single ascending dose study, followed by multiple ascending dose cohorts. Sentinel dosing precautious will be followed for all cohorts, with a pause for Safety Monitoring Committee review of safety data before progressing to the next dosing cohort.

2.5.2 Dose Selection Rationale

For the single dose cohorts, AP-PA02 is composed of three individual phages delivered at equivalent doses calculated by PFU. The proposed dose level in the SAD dose Cohort 1 is 3.3E9 PFUs per phage (1E10 PFUs per dose). The proposed dose level in the SAD dose Cohort 2 is 1E10 PFUs per phage (3E10 PFUs per dose). For a more common reference of dose level, the AP-PA02 single doses for Cohorts 1 and 2equate to 1.4 µg and 4.3 µg of protein, respectively.

For the multiple dose cohorts, AP-PA02 is composed of five individual phages delivered at equivalent doses calculated by PFU. The proposed dose level in the MAD dose Cohort 3 is 1.15E10 PFUs per phage (5.75E10 PFUs per dose) given twice daily, which is equivalent to 1.15E11 PFUs per day, for a total of 5.75E11 PFUs over five days of dosing. The proposed dose level in the MAD dose Cohort 4 is 3E10 PFUs per phage (1.5E11 PFUs per dose) given twice daily, which is equivalent to 3E11 PFUs per day, for a total of 3E12 PFUs over ten days of dosing. For a more common reference of dose level, the AP-PA02 multiple doses for Cohorts 3 and 4 both equate to 0.07 mg and 0.36 mg of protein, respectively.

To understand the potential for amplification to impact exposure we present an upper bound estimate of phage amplification based on the observation that AP-PA02 phages amplify *in vitro* with a burst size (number of progeny produced from one infected bacterium) of 100-150. We anticipate that *in vivo* amplification will be somewhat less efficient than *in vitro* amplification. Modeling from assumptions of a density of 1E7 *Pa* per gram of sputum, if a total volume of approximately 100 grams of sputum is assumed in the airways of a subject with CF, the total lung burden would be 1E9 total organisms (Hisert et al, 2017). If one presumes all 1E9 *Pa* bacteria were infected by the administered dose and an amplification of 100-150 phage/bacteria occurred, then the final maximal number of phage in the lung would be 1E11-1.15E11 PFU, regardless of the input dose since the bacterial numbers are the limiting factor. This theoretical maximum exposure generated with amplification is bracketed by the range of administered doses we plan to explore in this clinical study. The impact of amplification on phage exposures in humans has yet to be shown. Demonstrating phage levels and microbiological impact post-dosing are critical parts of this study essential to understanding phage exposure and future dosing regimens.

2.5.3 Proposed Doses

The combination of prior human exposure of AP-PA01 (predecessor product of AP-PA02) and preclinical data support the dosing scheme proposed in the SAD portion of this trial, starting at a single dose in Cohort 1 of 3.3E9 PFU per phage (1E10 PFU per dose) and escalating to a single dose in Cohort 2 of 1E10 PFU per phage (3E10 PFU per dose) of AP-PA02 administered by inhalation. Upon completion of each SAD dose level, the safety data will be reviewed by the Safety Monitoring Committee before initiating the next dose cohort. The MAD dosing scheme continues the assessment of safety of inhaled AP-PA02 across a schedule of two fractionated daily doses over 5 days for Cohort 3, and 10 days for Cohort 4. CF is a disease for which mucus impaction of airway segments is a prominent feature. Hence, intermittent obstruction of subsegmental bronchi and therefore poor regional ventilation may occur throughout the day. We hypothesize that dosing with inhaled AP-PA02 at two timepoints in a day could lead to better overall distribution of phage and improved efficacy than via a single administration. In Cohort 3, we will assess the safety of the 5-phage cocktail administrated at a similar dose per phage as was tested in Cohort 2.Cohort 3 dosing will be 1.15E10 PFU/phage (5.75E10 PFU per dose) administered BID, which equates to a total daily dose of 1.15E11 PFU per day, which will be administered for five consecutive days. If there are no clinically significant safety findings per SMC review of Cohort 3 clinical safety data, Cohort 4 will proceed. The total daily dose of phage will increase incrementally from Cohort 3's total daily dose of 1.15E11 PFU per day (5.75E10 PFU per dose BID) to Cohort 4's total daily dose of 3E11 PFU per day (1.5E11 PFU per dose BID), administered for ten consecutive days. Subjects will be monitored closely for adverse events and safety measures including sentinel dosing, stopping rules for individual subjects and the study itself as part of the study conduct. This MAD dosing scheme permits rational exploration of safety while increasing the likelihood of reaching an efficacious dosing regimen of inhaled AP-PA02, as assessed by microbiological endpoints, that will inform dose selection for exploration in further clinical trials.

Table 2 AP-PA02 Estimated Dose Levels By Cohort

Cohort	Each Dose PFUs (protein)	Daily Dose PFUs (protein)	Total Dose Per Treatment Course PFUs (protein)
1 (single dose)	1E10 (1.4µg)		
2 (single dose)	3E10 (4.3 µg)		
3 (BID x 5 days)	5.75E10 (6.9 µg)	1.15E11 (13.9 µg)	5.75E11 (69.4 µg)
4 (BID x 10 days)	1.5E11 (18.1 µg)	3E11 (36.2 µg)	3E12 (362.0 µg)

Based on the proposed doses in the MAD dose escalation scheme above, the total PFUs administered to the subject for the MAD cohorts 3 and 4 are 5.75E11 and 3E12, respectively, which equate to 0.07 mg and 0.36 mg of protein, respectively.

3 INVESTIGATIONAL MEDICINAL PRODUCT AND NEBULIZER

3.1 Investigational Medicinal Product

The investigational medicinal product (IMP), AP-PA02, is comprised of five bacteriophage drug products (DPs) which are manufactured by Armata Pharmaceuticals, Inc. (Armata). All processes are conducted under cGMP requirements including manufacturing, product storage, Quality Control (QC) raw materials, analytical and stability testing, and product release by Quality Assurance (QA). Bacterial fermentation, filtration and chromatography are performed in ISO 8 certified cleanrooms. Aseptic filling is performed in an ISO 5 certified isolator located within an ISO 7 certified cleanroom. QC analytical and stability testing are performed in a controlled environment. Where possible, single-use disposable parts (filters, tubing, vessels, etc.) are used to reduce the risk of contamination during the manufacturing process.

3.1.1 Drug Products

Each of the DPs is supplied as an opalescent to clear solution in a 2-mL clear glass vial closed with a sterile stopper and sealed with an aluminum crimped cap.

For the single dose cohorts, Cohorts 1 and 2, three of the five DPs will be combined for each dose (ARPA0003, ARPA0022, AND ARPA0034). Each vial contains 0.8 mLs of approximately 3E10 total PFU/mL, 132 mM NaCl, 1 mM $CaCl_2$ dihydrate, 10 mM $MgCl_2$ hexahydrate, 10 mM Tris Base, sterile water for injection solution with pH 7.4 adjusted with HCl.

For the multiple dose cohorts, Cohorts 3 and 4, all five DPs, formulated at a slightly higher concentration as shown below, will be combined for each dose. Each vial contains 0.9 mLs of approximately 5E10 total PFU/mL, 132 mM NaCl, 1 mM $CaCl_2$ dihydrate, 10 mM $MgCl_2$ hexahydrate, 10 mM Tris Base, sterile water for injection solution with pH 7.4 adjusted with HCl.

All five DPs are stable at 2–8°C.

Table 3 presents the composition of the five DPs as formulated for Cohorts 3 and 4, supplied as 5E10 PFU per mL, and the diluent/placebo.

Table 3 Composition of AP-PA02 and Diluent/Placebo for Cohorts 3 and 4

Component	ARPA0003 DP	ARPA0022 DP	ARPA0034 DP	ARPA0002 DP	ARPA0028 DP	Diluent/ Placebo
Phage ARPA0003 (PFU/mL)	5×10^{10}	0	0	0	0	0
Phage ARPA0022 (PFU/mL)	0	5×10^{10}	0	0	0	0
Phage ARPA0034 (PFU/mL)	0	0	5×10^{10}	0	0	0
Phage ARPA0002 (PFU/mL)	0	0	0	5×10^{10}	0	0
Phage ARPA0028 (PFU/mL)	0	0	0	0	5×10^{10}	0
Tris base (mg/mL)	1.2	1.2	1.2	1.2	1.2	1.2
Sodium chloride (mg/mL)	7.8	7.8	7.8	7.8	7.8	7.8
Calcium chloride dihydrate (mg/mL)	0.15	0.15	0.15	0.15	0.15	0.15
Magnesium chloride hexahydrate (mg/mL)	2.0	2.0	2.0	2.0	2.0	2.0
Hydrochloric acid	q.s. to pH 7.4	q.s. to pH 7.4	q.s. to pH 7.4	q.s. to pH 7.4	q.s. to pH 7.4	q.s. to pH 7.4
Water for injection	qs	qs	qs	qs	qs	qs

Abbreviations: mg = milligram; mL = milliliter; PFU = plaque forming unit; qs = quantity sufficient

3.1.2 Diluent and Placebo

Diluent/Placebo for IMP product dilutions is provided in 10 mL clear glass vials closed with a sterile stopper and sealed with an aluminum crimped cap. Each diluent vial contains 132 mM NaCl, 1 mM $CaCl_2$ dihydrate, 10 mM $MgCl_2$ hexahydrate, 10 mM Tris Base, sterile water for injection solution with pH 7.4 adjusted with HCl.

3.1.3 Packaging and Labeling

The bacteriophage DPs comprising AP-PA02 are packaged, labeled and released according to cGMP requirements appropriate for investigational products. Primary packaging for AP-PA02 is comprised of stoppered, crimped cap vials. The secondary packaging for the 3-phage configuration is a hard-cardboard box containing the 3 vials (one of each of the 3 phages), to be used only for the SAD cohorts 1 and 2. The secondary packaging for the 5-phage configuration for each phage component are cardboard cartons containing 6 vials of each phage (one type of phage per carton), to be used only for the MAD cohorts 3 and 4.

3.1.4 Drug Shipment and Storage

An initial supply of DP vials and placebo/diluent vials will be shipped refrigerated (2-8°C) to the site investigational pharmacy upon completion of site activation process. Re-supply will occur through the central inventory management system. The drug should be stored upright and refrigerated in the site pharmacy or a designated locked area at 2-8°C and protected from light until use.

Refer to the Study Manual for additional details on site activation, drug supply and the central inventory management system. Refer to the Pharmacy Manual for more detailed information regarding study drug receipt, storage, handling, preparation, dispensing and destruction.

3.1.5 Dose Preparation

The pharmacist (or other personnel qualified to prepare study drug for administration) at each site will receive study drug and will prepare and/or dilute the study drug according to the Pharmacy Manual for each administration. Pharmacy staff will be unblinded to subject treatment assignment (as assigned by the designated randomization system for the study). All other study staff, including the Investigator and subjects, will be blinded to study treatment assignment. Appropriate study drug dilutions or placebo will be prepared by an Unblinded Study Pharmacist, as detailed in the Pharmacy Manual. The prepared doses will be loaded into the nebulizer medication chamber by blinded clinic staff prior to administration to the subject.

Each dose, regardless of total phage (PFUs) per dose, will be prepared as a 3 mL loading volume for inhalation via the study nebulizer. The average residual volume left in the nebulizer chamber following completion of nebulization of the phage (or placebo) is less than 0.1 mL, with an average estimated delivered dose of approximately 97% (by volume) of the loading dose.

The final dose preparations of phage, regardless of total PFUs, as well as placebo, are isotonic and pH-neutral.

3.1.6 Dose Administration

Study drug doses will only be administered by a healthcare professional in an in-clinic setting. At-home dose administration will be allowed under supervision of a healthcare professional. Subjects will receive study drug by inhalation via the study-designated nebulizer. No other nebulizers should be used, and no other medications should be mixed with study drug in the study-designated nebulizer medication chamber.

Each prepared 3 mL dose, regardless of total phage (PFUs) per dose, should take approximately 5 minutes for complete nebulization, however, nebulization should continue until all DP has been administered.

3.1.7 Drug Accountability and Reconciliation

The Investigator must designate a research pharmacist or other staff member to be unblinded and maintain an inventory record of drugs received and dispensed. Used vials should be retained for drug accountability by the site monitor, unless prohibited by local procedures, in which case an alternative drug accountability process will be agreed upon with the Sponsor. Additional details on study drug handling will be provided in the Pharmacy Manual.

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

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

3.1.8 Overdose

The effects of overdose of this product are not known.

3.2 Nebulizer

An initial review of the literature indicated that vibrating mesh nebulizers would result in significantly less loss of potency (titer) than jet nebulizers (Carrigy et al. 2017). In-house testing of jet nebulizers compared to vibrating mesh nebulizers confirmed these results. (Refer to the Investigator's Brochure for additional details.)

3.2.1 eFlow Nebulizer System

The Investigational eFlow® Nebulizer System (PARI Respiratory Equipment) will be used to administration. Nebulizer assembly and use will be as described in the Instructions for Use (IFU) insert for the Investigational eFlow, as well as the study-specific Study Manual.

Study drug dose dilutions prepared by the unblinded pharmacist will be provided to the study staff (who are blinded to the treatment assignment) who will load the medication chamber of the eFlow nebulizer with the study drug dose specified by randomization. A new nebulizer handset will be provided for each subject. For the MAD cohorts, new nebulizer handset will be provided for each dose to eliminate the potential variability of cleaning the handset between doses for a given subject.

Study drug will be administered in the clinic by qualified site personnel via the designated study nebulizer, until all study drug solution has been administered. Complete administration of study drug/placebo, if uninterrupted, should take approximately 5 minutes (a minimal amount of study drug solution will remain in the nebulizer medication chamber—this is normal).

The Investigational eFlow used for this study should NOT be used to administer any other medication. The study drug for this study should NOT be administered using any other nebulizer or eFlow device; only the Investigational eFlow provided for study use.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Part 1 (SAD)

4.1.1 Primary Objective (SAD)

The primary objective of SAD portion of the study is to evaluate the safety and tolerability of a single dose of AP-PA02 administered by inhalation.

4.1.2 Primary Endpoint (SAD)

The primary endpoints of Part 1 of the trial are the incidence and severity of treatment-emergent adverse events (TEAEs), occurring from Day 1 pre-dose through the End of Study (EOS) Visit.

4.1.3 Exploratory Objectives (SAD)

Exploratory objectives of the SAD portion of the study include examining phage distribution and clearance, evidence of clinical efficacy, and the impact of phage therapy on the bacterial target after a single dose of AP-PA02 administered via inhalation.

4.1.4 Exploratory Endpoints (SAD)

- Phage titer profile in sputum, blood, and urine over time after a single dose of AP-PA02 administered via inhalation
- Change in FEV_1 (% predicted and absolute volume) from Day 1 pre-dose through EOS Visit
- Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) from Day 1 pre-dose through the EOS Visit
- Changes in the Cystic Fibrosis Respiratory Symptom Diary (CFRSD) and Chronic Respiratory Infection Symptom Score (CRISS) from Day 1 pre-dose through the EOS Visit
- Change in *P. aeruginosa* colony-forming units (CFU) per gram of sputum from Baseline through Visit 5
- Change in *P. aeruginosa* isolates' sensitivity to AP-PA02 and/or its individual components from Screening through the Visit 5
- Change in *P. aeruginosa* isolates' sensitivity to antipseudomonal antibiotics from Baseline through Visit 5

4.2 Part 2 (MAD)

4.2.1 Primary Objective (MAD)

The primary objective of the MAD portion of the study is to evaluate the safety and tolerability of multiple doses of AP-PA02 administered by inhalation.

4.2.2 Primary Endpoint (MAD)

The primary endpoints of Part 2 of the trial are the incidence and severity of treatment-emergent, adverse events (TEAEs), occurring from Day 1 pre-first dose through the End of Study Visit.

4.2.3 Secondary Objective (MAD)

The secondary objective is to explore *P. aeruginosa* recovery in sputum following multiple doses of AP-PA02 administered via inhalation.

4.2.4 Secondary Endpoint (MAD)

The secondary endpoint for the MAD portion of the trial is a change in *P. aeruginosa* colony-forming units (CFU) per gram of sputum from the Baseline Visit through approximately 14 days after the last dose of study drug.

4.2.5 Exploratory Objectives (MAD)

Additional exploratory objectives of the study include examining phage distribution and clearance, evidence of clinical efficacy, and the impact of phage therapy on the bacterial target.

4.2.6 Exploratory Endpoints (MAD)

- Phage titer profile in sputum, blood, and urine over time after multiple doses of AP-PA02 administered via inhalation
- Change in FEV_1 (% predicted and absolute volume) from Day 1 pre-dose through the EOS Visit
- Change in CFQ-R from Day 1 pre-dose through the EOS Visit
- Changes in the CFRSD and CRISS from Day 1 pre-dose through the EOS Visit
- Change in *P. aeruginosa* isolates' sensitivity to AP-PA02 and/or its individual components from Screening through approximately 14 days after the last dose of study drug.
- Change in *P. aeruginosa* isolates' sensitivity to antipseudomonal antibiotics from Baseline through approximately 14 days after the last dose of study drug.

4.3 Criteria for Evaluation

4.3.1 Safety and Tolerability

1. Adverse events (AEs)
2. Physical examination, including body weight
3. Vital signs
4. Electrocardiogram (ECG)
5. Spirometry (FEV_1, FVC and FEF_{25-75}) to evaluate for provoked bronchospasm
6. Clinical laboratory analyses for indications of toxicity: hepatic, renal
7. Immunogenicity (ADA)

4.3.2 Efficacy

Sputum *P. aeruginosa* density as measured in sputum samples at time points specified in the Schedule of Procedures.

4.3.3 Phage Recovery

Recovery of AP-PA02 will be based on AP-PA02 levels as measured in sputum and venous blood samples at time points specified in the Schedule of Procedures.

4.3.4 Exploratory

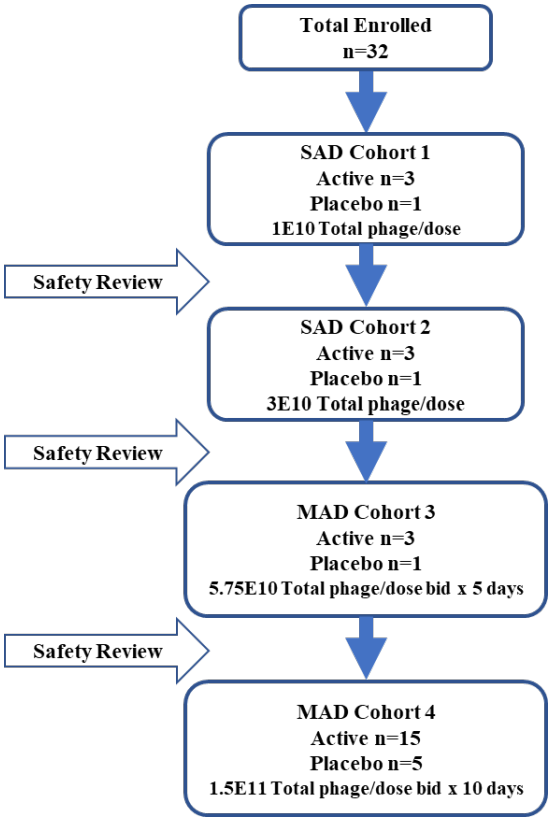
- Anti-pseudomonas antibiotic sensitivity of *Pa* isolates at specified time points during the study
- *In vitro* sensitivity of subject *Pa* isolates to AP-PA02 and/or individual phage components
- CFQ-R
- CFRSD-CRISS

5 STUDY DESIGN

This is a Phase 1b/2a, double-blind, randomized, placebo-controlled, single and multiple ascending dose study to evaluate the safety, tolerability and phage titer profile of AP-PA02 administered by inhalation. Figure 2 and Figure 3 depict the progression of dosing cohorts following safety review between cohorts.

Figure 2 Cohort Progression Schematic

Figure 3 Enrollment by Cohort Schematic



5.1 Ascending Dose Evaluations

5.1.1 Part 1: Single Ascending Dose (SAD) Evaluation

Part 1 will evaluate single ascending doses of AP-PA02 administered by inhalation in medically stable Cystic Fibrosis patients with pulmonary *P. aeruginosa* infection at time of Screening. A total of 8 subjects, 4 subjects in each of two sequential ascending dose cohorts,

will be randomized to receive either AP-PA02 or placebo administered via inhalation at the clinical site. Each cohort of 4 subjects will be randomized with 3 subjects in the treatment group and 1 subject in the placebo group. There will be a total of two placebo subjects enrolled across the two dose SAD cohorts.

Once enrolled, each subject will receive a single dose of AP-PA02 (or placebo) on Day 1. Subjects will be followed for safety and phage titer profiles for up to 4 weeks post-dose. The first two subjects of the same dose cohort will not be permitted to dose on the same day to allow for adequate safety monitoring between subjects.

The SMC will review all available safety data through Visit 4 for each SAD cohort (including any additional safety data from the prior SAD cohorts collected to date), before continuing to the next SAD dosing cohort.

See Section 5.3.3 Dose Escalation Rules for SAD cohorts.

5.1.2 Part 2: Multiple Ascending Dose (MAD) Evaluation

The MAD portion of the study will also be double-blinded, randomized, placebo-controlled, to evaluate the safety and efficacy of two dose levels of AP-PA02, enrolling 4 subjects into Cohort 3 and 20 subjects into Cohort 4.

Each cohort will be randomized at a 3:1 ratio.

Initiation of enrollment into the MAD portion of the study will be dependent on the positive recommendation and concurrence of the Sponsor following the SMC review following Cohort 2.

Cohort 3 of the MAD portion will be enrolled first, followed by Cohort 4. Once enrolled, each subject will receive one fractionated dose of AP-PA02 or placebo (one dose distributed over two administrations by inhalation in the same day), at least 6 hours apart, for five or ten consecutive days in the clinic for Cohorts 3 or 4, respectively. For Cohort 3, subjects will return to the clinic approximately 24 hours post-last dose for safety evaluations and phage titer sampling, for Visits 6 through 8, and End of Study Visit. For Cohort 4, subjects will return to the clinic approximately 24 hours post-last dose for safety evaluations and phage titer sampling, and on Visits 11 through 13, and End of Study Visit. A follow-up visit for safety and ADA titer will be performed at the End of Study Visit. The first two randomized subjects of each dose cohort will not be permitted to initiate dosing (Day 1) on the same day, to allow for adequate safety review.

The SMC will review all available safety data through Visit 7 for Cohort 3 (including any additional safety data from the SAD cohorts collected to date), before continuing to the next MAD dosing cohort. See Section 5.3.4 Dose Escalation Rules for MAD.

5.2 Dose Escalation

The single dose escalation scheme will test two dose levels administered once each, and the multiple dose escalation scheme will test two dose levels given as a fractionated dose over two administrations per day for five and ten consecutive days for Cohorts 3 and 4, respectively. As described in Section 3, the doses will be delivered to subjects via the PARI Investigational eFlow® device, corresponding to the dose escalation schemes are shown in Table 4.

Dose levels for the SAD cohorts shown below represent the total number of PFUs in the final 3-phage IMP formulation, with a 1:1:1 ratio of three phage components (ARPA0003, ARPA0022, ARPA0034), administered once per subject.

Dose levels for the MAD cohorts shown below represent the total PFUs in the 5-phage IMP formulation, to be delivered per dose administration with a 1:1:1:1:1 ratio of the five phage components (ARPA0003, ARPA0022, ARPA0034, ARPA0002, ARPA0028), the total daily fractionated dose given over two administrations per day, and the total combined PFU dose over five and ten consecutive days for Cohorts 3 and 4, respectively.

Table 4 MAD Dose Exposure

Cohort	Each Dose (estimated PFUs)	Total Daily Dose Fractionated over 2 Administrations per Day (estimated PFUs)	Total Dose Per Treatment Course (estimated PFUs)
1 (single dose)	1E10		
2 (single dose)	3E10		
3 (BID x 5 days)	5.75E10	1.15E11	5.75E11
4 (BID x 10 days)	1.5E11	3E11	3E12

Initiation of MAD Cohort 3 will be based on the safety profile of SAD Cohorts 1 and 2. Initiation of Cohort 4 will be based on the safety profile of Cohort 3. The first two subjects of each cohort will not be permitted be to initiate dosing (Day 1) on the same day, to allow for adequate safety review.

5.3 Dose Escalation Rules

5.3.1 Adverse Events of Interest

The AEs of Interest listed in Table 5 are AEs commonly seen with inhaled products. If AEs of interest occur at a Grade 3 level or higher in two or more subjects in a cohort, then an additional 4 subjects (3 active, 1 placebo) may be added to the cohort. Any of the Grade ≥ 3 toxicities shown in the table below, as well as any other respiratory AEs reported, will be evaluated and considered when making dose escalation decisions. If no additional subjects experience any Grade ≥ 3 AEs of Interest, dose escalation may proceed (if recommended by the SMC).

Table 5 Adverse Events of Interest

Adverse Events of Interest
Hypotension
Acute Bronchospasm
Hypoxia
Tachycardia
Acute Urticaria

5.3.2 Definition of Dose-Limiting Toxicity (DLT)

A Dose-limiting Toxicity (DLT) is defined as follows, determined by the Investigator as study drug related:

- Allergic reaction requiring urgent medical intervention
- Acute bronchospasm requiring urgent medical intervention
- Hypotension accompanied by other evidence of a systemic inflammatory reaction or sepsis
- Other acute AEs requiring urgent medical intervention

Allergic reactions may include local dermatitis, hives, urticaria, angioedema, or anaphylaxis. Appropriate treatment may include administration of antihistamines, prednisone, solumedrol, or epinephrine at the discretion of the assessing physician. Subjects diagnosed with a systemic allergic reaction requiring therapy will be discontinued from the study drug, but will be followed through the end of study.

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 AP-PA02.

The Investigator will base decisions to de-escalate to a lower dose, hold the dose (delay or skip), or discontinue study drug for an individual subject using the study-designated toxicity grading scale (see Section 12.3.1) in consultation and agreement with the Sponsor's Medical Monitor and/or designee. In addition to the toxicity grading scale, the Investigator should also review the stopping rules in Section 5.3.6 with regard to decreases in FEV_1.

If a subject experiences any acute AEs post-dose administration (regardless of causal relationship to study drug) that have not resolved by the time is to be discharged home on Day 1, it will be left up to the discretion of the Investigator to admit the subject for overnight continued observation, if in the best interest of the subject.

5.3.3 Dose Escalation Rules for SAD

For the single dose cohorts, dose escalation to the next cohort may occur upon recommendation of the SMC after the safety data from all subjects through Day 8 for a given cohort.

5.3.4 Dose Escalation Rules for MAD

For the multiple dose cohorts, dose escalation to the next cohort may occur upon recommendation of the SMC after the safety data from all subjects through Visit 7 for Cohort 3.

For the multiple dose cohorts, subjects who experience a DLT should be discontinued from study drug but are encouraged to remain in the study through the End of Study Visit. Appropriate safety evaluations should be performed within 24 hours of the DLT.

Dose escalation will occur based on the positive recommendation of the safety data as assessed by the SMC at the end of each cohort.

5.3.5 Criteria for Study Drug Discontinuation

Subjects should be continued on study treatment unless individual Stopping Rules have been met as outlined below. Study drug should be stopped and subject(s) advised regarding available treatment options.

When study drug is discontinued in the MAD cohort, appropriate safety evaluations should be performed, and the subject should be followed for safety through the End of Study visit.

5.3.6 Stopping Rules

5.3.6.1 Stopping Rules for Study

The SMC will evaluate the safety data through Visit 4 for SAD cohorts and Visit 7 for MAD Cohort 3, and 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. Study enrollment and dosing should be paused for SMC review for the following occurrences which can be cause for termination of the Study:

a) One or more subjects experience a serious adverse (SAE) or Grade 4 adverse event considered at least possibly related to study drug.
b) Two or more subjects experience the same or similar Grade 3 adverse event (AE) of the same system organ class (SOC).
c) Two or more subjects experience Grade 3 or greater hypersensitivity reactions (e.g. difficulty breathing, rash, hypotension).

5.3.6.2 Stopping Rules for Individual Subjects

a) Individual subjects experiencing a DLT (see Section 5.3.2 Definition of Dose-Limiting Toxicity) will result in discontinuation of study drug administration (i.e. either incomplete administration of an individual dose in the SAD, or incomplete administration of an individual dose and discontinuation of further dosing in the MAD). These subjects will continue to be followed for safety through the End of Study visit.

b) For individual subjects, any of the following will result in permanent discontinuation of study drug. If study drug is discontinued for any of these stopping rules, administration will not be resumed, even after resolution of the event.

- Any serious adverse event (SAE) suspected of being possibly, probably or definitely related to study drug
- Any Grade ≥ 3 AE suspected of being related to study drug
- Acute bronchospasm defined as a decrease in absolute FEV_1 volume of ≥ 15% accompanied by symptoms requiring medical intervention, occurring from baseline value up to four hours following study drug administration, persisting following administration of a short-acting bronchodilator
- Acute pulmonary exacerbation confirmed by the Investigator based on clinical findings including fever, weight loss and/or generalized malaise associated with increased dyspnea, cough, change in sputum quantity or quality, or new infiltrate/consolidation on imaging
- Unacceptable toxicity considered by the Investigator to be related to study drug treatment
- Further treatment is deemed to be unsafe in the Investigator's clinical judgment. The decision to discontinue a subject may also result from any clinically significant alteration in any clinical or laboratory finding
- If at any time the subject fails to follow the requirements of the protocol
- The subject withdraws consent. Subjects may withdraw from the study at any time without repercussion to their treatment or affiliation with their healthcare providers.

For individual subjects in the MAD cohorts, if the pre-first dose absolute FEV_1 volume on a given dosing day is < 15% of the baseline absolute FEV_1 volume (the pre-first dose value on Day 1), dosing should be held for that day and resumed the following day. If on the subsequent day the FEV_1 volume is still <15% of the baseline value on Day 1, study drug should be discontinued permanently, and the subject should continue to be followed for safety through the End of Study visit.

5.4 Study Completion and Discontinuation Criteria

5.4.1 Study Completion

Subjects who receive all planned study drug doses and complete all post-dose evaluations will be considered to have completed the study.

Subjects who were randomized into a SAD cohort, and who received at least 1 study drug dose are not eligible to participate in a subsequent SAD cohort or in a MAD cohort.

5.4.2 Study Withdrawal

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

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

Subjects withdrawn from SAD cohorts should have all assessments conducted at the End of Study Visit at the time of withdrawal. Subjects withdrawn from MAD cohorts should have all assessments conducted at the End of Treatment Visit as well as the End of Study Visit, for safety monitoring purposes.

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

Given the proposed mechanism of action of AP-PA02, it could be anticipated that subjects could experience a change in baseline cough, change in sputum quality, or change in sputum volume. A pulmonary exacerbation should be considered if these symptoms are accompanied by fever, body weight loss, and/or generalized malaise. If a pulmonary exacerbation is diagnosed, appropriate interventions including appropriate additional antibiotics should be prescribed by the Investigator or treating physician. Subjects diagnosed with a pulmonary exacerbation requiring the addition of antibiotics will be discontinued from study drug, but will continue to be followed for safety through the End of Study visit.

5.4.3 Study Termination

If the Sponsor, SMC, Sponsor's Medical Monitor or designee, study monitor, or appropriate regulatory officials discover conditions arising during the study that indicate that the study

should be halted or that a study center should be terminated, this action may be taken after appropriate consultation. Termination may occur in accordance with the clauses contained in the site's executed clinical trial agreement. Armata Pharmaceuticals, Inc. reserves the right to discontinue the trial prior to enrollment of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons.

If the clinical development of AP-PA02 is discontinued, the Sponsor shall immediately inform all trial Investigators/institutions and regulatory authorities. Study termination and follow-up will be performed in compliance with the conditions set forth in the ICH E6(R2) on GCP guidelines and local regulatory requirements.

6 STUDY POPULATION

6.1 Selection of Subjects

Subjects with cystic fibrosis and chronic pulmonary *Pa* infection who meet all inclusion and exclusion criteria will be eligible for participation in this study.

6.1.1 Inclusion Criteria

1. Able and willing to comply with the protocol and provide written informed consent prior to study-specific procedures
2. Male or female ≥ 18 years old at the time of Screening
3. Body mass index (BMI) of ≥ 18 kg/m^2
4. Must have confirmed diagnosis of cystic fibrosis, as documented by one of the following criteria:
   a. Sweat chloride ≥ 60 mEq/L by quantitative pilocarpine iontophoresis test performed at or prior to Screening -OR-
   b. Known disease-causing mutations in the CFTR gene on each chromosome.
5. Clinically stable with no significant changes in health status within the 7 days prior to and including the Screening Visit
6. Evidence of chronic pulmonary *Pa* infection. Evidence includes one or more of the following:
   a. Microbiological evidence of pulmonary *Pa* infection within the last 24 months
   b. Current utilization of chronic-suppressive inhaled antibiotics for *Pa*
   c. Oral or parenteral antipseudomonal therapy administered within the last 2 years
7. Willing to undergo sputum induction procedures at Screening, Baseline and at designated time points during the study, and willing to provide expectorated sputum samples at all other timepoints (for subjects who are able to expectorate).
8. Must have $\geq 10^4$ CFU of *Pa* per gram of induced sputum obtained at Screening
9. Subject's *Pa* isolates are susceptible to AP-PA02, based on morphotypes obtained from induced sputum obtained at Screening.
10. For SAD: $FEV_1 \geq 60\%$ of predicted normal for age, gender, race and height [using Global Lung Function Initiative (GLI) standards] at Screening (regardless of the timing of the most recent prior administration of short-acting bronchodilator).

    For MAD: $FEV_1 \geq 40\%$ of predicted normal for age, gender, race and height [using Global Lung Function Initiative (GLI) standards] at Screening (regardless of the timing of the most recent prior administration of short-acting bronchodilator).

11. Stable lung function, determined by the Investigator, provided that the FEV_1 at the Baseline Visit has not decreased by more than 5% compared to the FEV_1 measured at Screening.
12. Able to reproducibly perform pulmonary function tests per ATS/ERS standards.
13. For subjects to be enrolled into Part 1 of the protocol (SAD), dosing relative to their inhaled antibiotics schedule is not restricted; subjects participating in Part 1 SAD may schedule Day 1 at any time. For subjects to be enrolled into Part 2 of the protocol (MAD), if on inhaled antibiotics for chronic suppression of *P. aeruginosa:*
    a. Subjects on a single, chronically-administered inhaled antipseudomonal antibiotic or on two or more alternating inhaled antipseudomonal antibiotics, must remain on the same regimen from Screening through the end of the study. Day 1 can be scheduled at any time.
    b. Subjects on a chronically-administered routine of an intermittent inhaled antipseudomonal antibiotic (one month "on", one month "off") must be at least 6 days and not more than 17 days into the on- or off-month on Day 1.
    c. Subjects on a chronically-administered routine of inhaled antipseudomonal antibiotic, not following a monthly on/off inhaled antibiotic schedule, may be enrolled provided the subject is on the on-cycle of the inhaled antibiotic from the Baseline Visit through approximately 14 days after the last study drug dose.
    d. Subjects not on chronically-administered inhaled antipseudomonal antibiotics may be scheduled for Day 1 at any time.
14. Creatinine clearance > 80 mL/min, as calculated by Cockcroft-Gault equation based on actual body weight
15. Ability to comply with study visits and study procedures as judged by the investigator
16. Female subjects of childbearing potential must agree to use a highly effective method of birth control (defined as those, alone or in combination, that result in a low failure rate [i.e. less than 1% per year]) from Day 1 through 60 days following the last dose of study drug.
17. Male subjects must agree to use barrier contraception (i.e. condoms) from Day 1 through 60 days following the last dose of study drug.
18. The following criteria relate to acceptable laboratory values at Screening.
    a. Hemoglobin > 8 g/dL
    b. WBC < 14,000/µL
    c. Platelet count > 150 x 10^3/µL
    d. Prothrombin time (PT), International Normalized Ratio (INR) and partial thromboplastin time (PTT) within normal limits. Subjects with values outside the normal range may be permitted if the value is not clinically significant in the opinion of the Investigator, with concurrence from the Study Medical Monitor and/or Sponsor designee.

6.1.2 Exclusion Criteria

1. Decrease in body weight within 90 days prior to Screening that is considered clinically significant by the Investigator
2. Abnormal vital signs at Screening: heart rate > 110 beats per minute (bpm) at rest; systolic blood pressure > 160 or < 90 mmHg; respiration rate > 24 bpm; and SpO_2 < 92% at rest on room air
3. Subject history of, or patient-reported family history of, prolonged QT syndrome; or a QTc interval > 450 msec (males) or > 470 msec (females) using Fredericia's formula (QTcF)
4. Use of supplemental oxygen during the day at rest
5. Serum albumin < 2.5g/dL
6. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values greater than 3X the upper limit of normal (ULN) at Screening.
7. Oral or parenteral antibiotics received within 30 days prior to the Baseline Visit for acute pulmonary exacerbation. Inhaled antibiotic use for chronic suppression of *P. aeruginosa* is acceptable.
8. Any infection as determined to be clinically significant in the opinion of the Investigator with concurrence from the Sponsor's Medical Monitor and/or designee that results in receiving new systemic antimicrobial therapy within 30 days prior to the Baseline Visit.
9. Currently receiving anti-pseudomonal antibiotic treatment for acute sinusitis.
10. Currently receiving systemic corticosteroids at a dose greater than the equivalent of 10 mg/day of prednisone
11. Currently receiving treatment for active infection with nontuberculous mycobacteria (NTM), *Staphylococcus aureus,* or *Burkholderia cepacia* complex lung infection.
12. Currently receiving treatment for aspergillosis or ABPA (allergic bronchopulmonary aspergillosis)
13. Subject initiated on a CFTR potentiator/corrector therapy, such as Trikafta®, less than 90 days prior to Screening.
14. Acquired or primary immunodeficiency syndromes
15. Active pulmonary malignancy (primary or metastatic) or any malignancy requiring chemotherapy or radiation therapy within one year prior to screening or anticipated during the study period
16. History of lung transplantation
17. Hemoptysis of greater than 30 mLs (cumulative) within 90 days prior to Day 1 or hospitalization for hemoptysis within 6 months of Day 1
18. Female pregnant or breastfeeding

19. Use of any investigational device or administration of any investigational products within 8 weeks or five therapeutic half-lives prior to study Day 1, whichever is longer.
20. Smoking more than 10 cigarettes or 2 cigars or 2 pipes per day, or nicotine equivalent from vaping, from within 3 months prior to screening through the end of the study.
21. Presence or medical history of clinically significant condition which precludes study participation or prevents determination of outcome measures.
22. Any severe, acute, or chronic medical or psychiatric condition, laboratory abnormality, or other condition other than CF that, in the opinion of the Investigator, participation in the study is not in the best interest of the patient, puts the subject at undue risk, interferes with the results of the study, or makes the subject otherwise unsuitable for study participation.
23. Prior participation in study AP-PA02-101. Subjects previously enrolled in this study and received at least one dose of study drug are ineligible for re-enrollment.

7 CONCOMITANT MEDICATIONS AND ANCILLARY THERAPY

7.1 Inhaled Antipseudomonal Antibiotics

7.1.1 Part 1 SAD Subject Scheduling

Subject dosing relative to their inhaled antibiotics schedule is not restricted. Subjects participating in Part 1 SAD may schedule Day 1 at any time.

7.1.2 Part 2 MAD Subject Scheduling

Initiation of subject dosing (Day 1) is limited for subjects participating in Part 2 MAD relative to their inhaled antibiotics schedule, as described below.

7.1.2.1 Chronic Continuous Therapy

Subjects who are on chronically-administered inhaled antipseudomonal antibiotics on a continuous basis (the same inhaled antibiotic, no interruption of therapy or use of alternate antibiotic) should remain on the same therapy from Screening through the end of the study. Day 1 may be scheduled at any time during the subject's inhaled antipseudomonal antibiotic regimen.

7.1.2.2 Chronic Alternating Therapy (CAT)

Subjects who are on a chronically-administered routine of two or more alternating antipseudomonal antibiotics should remain on the same therapy from Screening through the end of the study. Day 1 may be scheduled at any time during the subject's inhaled antipseudomonal antibiotic regimen.

7.1.2.3 Chronic Intermittent Therapy (CIT)

- Subjects who are on a chronically-administered routine of intermittent antipseudomonal antibiotics ("on" one month, "off" one month) should be scheduled to initiate study drug dosing (Day 1) and must be at least 6 days and not more than 17 days into the on- or off-month on Day 1.
- Subjects not following a monthly on/off inhaled antibiotic schedule may be enrolled provided the subject is on the on-cycle of the inhaled antibiotic from the Baseline Visit through approximately 14 days after the last study drug dose.

7.2 Chest Physiotherapy

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

7.3 Order of Therapies

Prior to study drug dosing on a given day, any concurrent treatments that the subject receives at baseline should be administered in the following order: Long- and/or Short-acting bronchodilator, mucolytic therapy (e.g. Pulmozyme), chest physiotherapy (airway clearance technique), inhaled corticosteroid, inhaled antibiotics, and lastly, administration of study drug. Administration of these therapies should be performed in the same order each dosing day, prior to spirometry and study drug dosing.

Ancillary therapy regimens and airway clearance techniques should remain consistent throughout the study period.

7.4 CFTR Potentiators/Correctors

Subjects should not be initiated on CFTR potentiators/correctors within 90 days prior to Screening, or during the study. Changes to such therapy prior to or during the study are permitted, with concurrence from the study Medical Monitor and/or Sponsor designee, and should be documented in the eCRF.

7.5 Ancillary Therapy

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

7.5.1 Premedication

For subjects whose standard CF medications include a short-acting β-agonist (SABA) and/or a long-acting β-agonist (LABA), the most recent time of administration of the SABA and/or LABA prior to each study drug dose should be recorded.

7.5.2 Prohibited Concomitant Medications

Oral corticosteroid medications may not be used prophylactically with any dose of study drug. Chronic administration of oral corticosteroids at a stable dosage up to 10 mg/day for at least 30 days prior to enrollment are permitted. The reason(s) for ancillary therapy, including dosage and date(s) of treatment, will be recorded in the source documents. Subjects started on oral corticosteroids after randomization should be withdrawn from study drug, and should remain on study through the End of Study visit.

7.6 Adequate Forms of Birth Control

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

until becoming post-menopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Highly effective methods of birth control include:

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

Birth control measures must be employed during the time of participation (beginning at the Screening Visit) in this trial. Protections against pregnancy must be continued for at least 60 days after the last dose of study drug.

A man is considered fertile after puberty unless permanently sterile by bilateral orchiectomy. Male subjects with CF with medical confirmation of azoospermia and/or infertility will be considered permanently sterile. A man who is fertile should use a condom during treatment and until 60 days after the last dose of study drug.

7.7 Adverse Reaction Management

AEs in the study will be treated with appropriate therapies. Acute bronchospasm (defined as a $\geq$ 15% decrease in FEV_1 absolute volume from pre-dose (first dose) to post-dose on a given dosing day) should be treated with treatment cessation and inhaled β2 agonists; IV solumedrol or other agents should be administered as deemed appropriate by the Study Investigator. Additional supportive care should be provided as necessary by qualified staff with emergency resuscitation equipment.

A Grade 3 adverse reaction requires interruption of dosing in the SAD and MAD cohorts and permanent discontinuation of study drug in the MAD cohorts.

8 EVALUATIONS BY VISIT

All tests and procedures are detailed in Appendix 1, Schedule of Assessments. Refer to these appendices for the required assessments for each study day. Throughout the protocol, the term "baseline" is used to refer to tests or procedures performed at screening, Baseline Visit, or on Day 1 prior to the time of administration of the first dose.

8.1 Visit and Assessment Windows

The flexibility regarding scheduling of study days relative to Day 1 are specified in the Schedule of Study Procedures tables in the Appendices. The timing of assessments, procedures and sample collections outlined in the protocol are nominal times. It is understood that in the phase 1 setting, actual times will approximate rather than match the nominal times exactly. Actual times are to be recorded in the source documentation and in the case report forms (CRFs), and, if any time points are missed, the reasons should also be recorded.

The MAD doses should be administered on consecutive days. Missed doses are to be recorded as such. If dosing is held and postponed to the next day, doses should be recorded as "delayed", along with the reason for the delayed administration. If the MAD Day 2 doses are delayed, and are administered on Day 3, the doses originally scheduled for administration on Day 3 will be then administered on Day 4, and so on. All subsequent study days will be conducted as outlined in the Table of Assessments, but pushed out by a day (Day 4 procedures will be conducted on Day 5, etc.).

Dosing delays should not exceed more than one day. If greater than one day of delay of dosing occurs, the subject should be withdrawn from study drug, but should continue to be followed for safety through the End of Study Visit.

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

8.2 Screening Visit (All Cohorts)

A screening log of all consented subjects will be kept at each site. Subject screening will be conducted up to 35 days prior to study drug dosing (Day 1). Screening evaluations may be completed over several days, if necessary. If the screening period extends beyond 35 days, the potential subject will be considered a screening failure, but may be re-screened at a later date.

All screening evaluations must be reviewed by the Investigator to establish subject eligibility before dosing the subject for this study. Local laboratory results will determine subject eligibility for laboratory criteria, except for presence of *Pa* in sputum at Screening, and *Pa* isolate susceptibility to AP-PA02 (performed at a central laboratory). Subjects may be allowed to submit a repeat induced sputum sample for eligibility (if time allows during the 35-day Screening Period), if the initial sample is unusable or negative for *Pa*.

8.3 Baseline Visit (All Cohorts)

The Baseline Visit will be scheduled between Day -7 and Day -1 (inclusive) relative to Visit 1 Day 1 for all cohorts. Screening evaluations cannot be combined with evaluations performed as part of the Baseline Visit, unless results are obtained and reviewed by the Investigator, and eligibility can be confirmed prior to randomization.

9 STUDY PROCEDURES

Safety parameters will be assessed by monitoring AEs, vital signs, oximetry, laboratory data (chemistries, hematology and urinalysis), ECGs, pulmonary function (spirometry), and physical examinations. Subjects not fulfilling the eligibility criteria, or were randomized but not dosed, may be rescreened for participation if their eligibility characteristics change. Screening procedures that fall within the screening window do not need to be repeated. Subjects that previously failed screening, or were randomized but not dosed, may undergo re-screening under a new Subject Number for confirmation of eligibility and enrollment into the study at a later date, with approval from the study Medical Monitor and/or Sponsor designee.

9.1 Vital Signs

Blood pressure, heart rate, respiration rate, and temperature will be measured at rest in a sitting position. At Screening, if vital signs measured are not within the stated eligibility limits, it is permissible to allow the subject to rest at least another 10-15 minutes and repeat the vital signs measurements.

For SAD cohorts, vital signs will be measured at Screening, Baseline, Day 1 pre-dose, 10, 30 and 60 minutes post-dose, and 2, 4 and 7 hours post-dose. Vital signs will also be measured at Visits 2, 3, 4, 5, and 6.

For MAD Cohort 3, vital signs will be measured at Screening, Baseline, and at the following timepoints on dosing days (see also Appendix 1 Tables D and E):

Table 6 MAD Cohort 3 Vital Signs Timepoints on Dosing Days 1-5

Visit	Day	Dose	Timepoints on Dosing Days
1	1	1	Pre-dose, 10 minutes and 60 minutes post-dose
		2	Pre-dose (approximately 6 hours post-dose 1), 1-hour post-Dose 2
2	2	3	Pre-dose, 10 minutes and 60 minutes post-dose
		4	Pre-dose (approximately 6 hours post-Dose 3), 1-hour post-Dose 4
3	3	5	Pre-dose, 10 minutes and 60 minutes post-dose
		6	Pre-dose (approximately 6 hours post-Dose 5), 1-hour post-Dose 6
4	4	7	Pre-dose, 10 minutes and 60 minutes post-dose
		8	Pre-dose (approximately 6 hours post-Dose 7), 1-hour post-Dose 8
5	5	9	Pre-dose, 10 minutes and 60 minutes post-dose
		10	Pre-dose (approximately 6 hours post-Dose 9), 1-hour post-Dose 10

For MAD Cohort 3, vital signs will also be measured at Visits 6, 7, 8, and 9.

For MAD Cohort 4, vital signs will be measured at Screening, Baseline, and at the following timepoints on dosing days (see also Appendix 1 Tables G, H and I):

Table 7 MAD Cohort 4 Vital Signs Timepoints on Dosing Days 1-10

Visit	Day	Dose	Timepoints on Dosing Days
1	1	1	Pre-dose, 10 minutes and 60 minutes post-dose
		2	Pre-dose and 1-hour post-Dose 2
2	2	3	Pre-dose and 60 minutes post-dose
		4	Pre-dose and 1-hour post-Dose 4
3	3	5	Pre-dose and 60 minutes post-dose
		6	Pre-dose and 1-hour post-Dose 6
4	4	7	Pre-dose and 60 minutes post-dose
		8	Pre-dose and 1-hour post-Dose 8
5	5	9	Pre-dose and 60 minutes post-dose
		10	Pre-dose and 1-hour post-Dose 10
6	6	11	Pre-dose and 60 minutes post-dose
		12	Pre-dose and 1-hour post-Dose 12
7	7	13	Pre-dose and 60 minutes post-dose
		14	Pre-dose and 1-hour post-Dose 14
8	8	15	Pre-dose and 60 minutes post-dose
		16	Pre-dose and 1-hour post-Dose 16
9	9	17	Pre-dose and 60 minutes post-dose
		18	Pre-dose and 1-hour post-Dose 18
10	10	19	Pre-dose and 60 minutes post-dose
		20	Pre-dose and 1-hour post-Dose 20

For MAD Cohort 4, vital signs will also be measured at Visits 11, 12, 13, and 14.

9.2 Oximetry

Digital oximetry (SpO_2) will be measured at rest in a sitting position. Oximetry will be measured at all timepoints where vital signs are measured.

9.3 Local Laboratory Evaluations

Safety laboratory evaluations will be performed according to the study schedule, using the clinical site's local laboratory. Repeat of Screening laboratory evaluations are permissible to confirm eligibility.

Blood samples for clinical laboratory testing (serum chemistries and hematologies) obtained pre-dose on Day 1 (for all cohorts), if abnormal and clinically significant at Baseline, results are to be reviewed by Investigator prior to administration of study drug.

Safety laboratory samples will be obtained at Screening and Baseline, and at the additional following timepoints:

- For SAD cohorts: Visits 2, 3, 4, and 5.

- For MAD Cohort 3: Visits 2, 5, 7, and 8. Blood samples for clinical laboratory testing to be obtained pre-first dose on Visits 2 and 5, and results reviewed by Investigator prior to administration of study drug on those days.

- For MAD Cohort 4: Visits 2, 10, 12, and 13. Blood samples for clinical laboratory testing to be obtained pre-first dose on Visits 2 and 10, and results reviewed by Investigator prior to administration of study drug on those days.

9.3.1 Serum Chemistry

Serum chemistries will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphorus, ALT, AST, alkaline phosphatase, albumin, bilirubin (total and direct). Creatinine clearance is to be calculated using the Cockcroft-Gault equation adjusted for actual body weight.

9.3.2 Hematology

Hematologies will include a complete blood count (CBC), which includes hematocrit, hemoglobin, platelet count, and white blood count (with absolute and/or relative differential, as reported by the site's local laboratory).

9.3.3 Coagulation

Coagulation testing (PT-INR, PTT) to be performed at Screening for eligibility.

9.3.4 Urine Testing

9.3.4.1 Urinalysis

Urinalysis will be performed at time points designated by the study schedule (and listed below) at the local laboratory. Urinalysis will be performed by visual inspection and dipstick, and will include color and appearance, specific gravity, pH, protein, glucose, occult blood, ketones, bilirubin, leukocyte esterase, nitrite, and urobilinogen. In addition, microscopic analyses will be performed on samples with abnormal dipstick results.

Urine samples for urinalysis to be obtained pre-dose on Day 1 (for all cohorts), if abnormal and clinically significant at Baseline, and results reviewed by Investigator prior to administration of study drug.

Urine samples will be obtained at Screening and Baseline, and at the additional following timepoints:

- For SAD cohorts: Visits 2 and 5.
- For MAD Cohort 3: Visits 6 and 8.
- For MAD Cohort 4: Visits 10 and 13.

9.3.4.2 Pregnancy

For female subjects, a pregnancy test will be obtained as designated by the study schedule. Urine or serum pregnancy testing are allowed.

9.4 Central Laboratory Evaluations

9.4.1 Serology

Serum samples will be obtained at specified time points during the study to determine if titers of anti-drug antibodies (ADA) are detectable. Serology samples will be batch-analyzed at the end of the study and will be stored for additional testing if titers are detected.

In the current COVID-19 environment, it is possible that exposure to SARS-CoV2 may have an impact on the outcomes measured in this study. Therefore, serum samples will be obtained at specified time points during the study and stored for possible future testing for the presence of SARS-CoV2 antibodies.

Serology samples to be collected at the following timepoints:

- For SAD cohorts: Baseline, and Visits 5 and 6.
- For MAD Cohort 3: Baseline, and Visits 8 and 9.
- For MAD Cohort 4: Baseline, and Visits 13 and 14.

9.4.2 Sputum Microbiology

Sputum for microbiology will be obtained as designated by the study schedule and processed at a central laboratory for all visits. *Pseudomonas aeruginosa* isolates obtained from sputum samples at all visits will be frozen for possible future genotyping analysis. No subject (human) samples will be retained for any genetic analysis.

Collection of sputum via induction for all subjects (regardless of their ability to spontaneously expectorate sputum), will be performed per standardized methodology at the timepoints specified in the Schedule of Procedures tables in Appendix 1. Standardized sputum induction methodology to be detailed in the Study Manual.

For expectorated sputum collection, subjects may be asked to provide first morning samples expectorated before a given clinic visit or the subjects may provide the expectorated sputum sample during the clinic visit. Samples collected at home by the subject should ideally be collected prior to administration of any inhaled antipseudomonal antibiotic. Subjects will be provided sputum collection vessels and insulated transport containers in which to carry their specimens to the clinic.

9.4.3 Phage Recovery Evaluations

Samples for phage recovery analyses will be collected as detailed in Appendix 1. Detailed instructions for sample collection and shipment to the central lab for analysis will be provided in the study laboratory manual.

9.4.3.1 Blood

Blood samples, when scheduled at time points when safety labs and phage titer samples are also to be collected, safety lab samples are to be collected first, followed by phage titer samples.

9.4.3.2 Sputum

Expectorated and/or induced sputum samples for phage titers can be difficult to obtain at the specified time points. It is suggested that samples be collected in conjunction with spirometry, as often spirometry maneuvers can provoke coughing and sputum expectoration.

9.4.3.3 Urine

Urine samples for phage recovery will be obtained at the visits indicated in the Schedule of Assessments table using provided collection containers. Date and time will be recorded for each urine sample collection at the designated time points.

9.5 Electrocardiogram (ECG)

A 12-lead ECG will be performed locally at the site, and obtained at Screening, and pre-dose and 1 hour post dose on Day 1 for all subjects enrolled in SAD cohorts. For subjects enrolled into MAD cohorts, a 12-lead ECG will also be performed at the End of Study Visit.

The Fridericia formula (Vandenberk et al. 2016) for calculating QTc will be used (QTcF).

9.6 Spirometry

Spirometry will be performed per ATS/ ERS Standards (Miller et al. 2005; Pellegrino et al. 2005; Wanger et al. 2005; Quanjer et al. 2012; Graham et al. 2019), and evaluated locally at the clinical study site. FEV_1, FVC, and FEF_{25-75} will be collected. Actual liter values will be recorded. Details regarding spirometry procedures and standards will be included in the Study Manual.

For SAD cohorts, spirometry will be performed at Screening, Baseline, Day 1 pre-dose; 30 minutes, 60 minutes and 7 hours post-dose. Spirometry will also be performed at Visits 2, 3, 4, 5, and 6.

For MAD cohorts, spirometry will be performed at Screening, Baseline, and at the following timepoints on dosing:

For MAD Cohort 3 (Visits 1-5), (See Appendix 1, Tables D and E):

- Visit 1: Pre-Dose, 30 minutes, and at 2 and 7 hours post-first dose (approximately 1 hour post-Dose 2)
- Visits 2 through 5: Pre-first dose, 30 minutes and 7 hours post-first dose of the day (approximately 1 hour post-second dose of the day)
- Spirometry will also be performed at Visits 6, 7, 8, and 9.

For MAD Cohort 4 (Visits 1-4 and 8-10), (See Appendix 1, Tables G, H, and I):

- Visit 1: Pre-Dose 1, 30 minutes, and at 2 and 7 hours post-first dose (approximately 1 hour post-Dose 2)
- Visits 2 through 4, and Visits 8 through 10: Pre-first dose, 30 minutes and 7 hours post-first dose of the day (approximately 1 hour post-second dose of the day)
- Spirometry will also be performed at Visits 11, 12, 13, and 14.

9.7 Physical Examination

Complete physical examinations (urogenital exams not required) will be performed at Screening, Baseline and Visit 5 for subjects enrolled in the SAD cohorts. For MAD Cohorts, complete physical examinations will be performed at Screening, Baseline, and/or at the EOS Visit Symptom-directed physical exams will be performed at all other time points, as indicated by the study schedule.

9.8 Height and Weight

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

9.9 Sweat Chloride and Genotyping

Documentation of cystic fibrosis by either of the following is required for study eligibility:

1. Sweat chloride by pilocarpine iontophoresis of ≥ 60 mmol/L performed at or prior to Screening -OR-
2. Documentation of known disease-causing mutations in the CFTR gene on each chromosome.

If historical sweat chloride or CFTR genotyping results are not available, a sweat chloride test or CFTR genotyping should be performed to determine study eligibility. If the historical (or Screening) sweat chloride value is ≥ 30 mmol/L but less than 60 mmol/L, the subject must also have CF genotyping performed, and have at least one disease-causing mutation in the CFTR gene on each chromosome.

9.10 CFQ-R

The CFQ-R subject health-related quality of life questionnaire (Quittner et al. 2005) will be administered using the self-administered format (Adult version) [Appendix 2], according to the study schedule for all subjects. The CFQ-R will be administered prior to any other test or procedure on each of the required study days. The CFQ-R responses will be entered into the eCRF by clinical site staff.

9.11 CFRSD-CRISS

The Cystic Fibrosis Respiratory Symptom Diary – Chronic Respiratory Infection Symptom Score (CFRSD-CRISS) is an 8-item patient-reported outcome (PRO) symptom measure that is part of the Cystic Fibrosis Respiratory Symptom Diary [Appendix 3]. The CFRSD-CRISS is designed to evaluate the effect of treatment on the severity of symptoms of respiratory infection in adults and adolescents (> 12 years) with CF and a chronic respiratory infection (Goss et al. 2009). Symptoms assessed in the CFRSD-CRISS are: difficulty breathing, cough, cough up mucus, chest tightness, wheeze, feeling feverish, tired, and chills/sweats.

The CFRSD daily diary will be dispensed to study subjects starting at the Baseline Visit for all subjects. Subjects will be instructed to bring the diary to the clinic for each subsequent study visit and will be collected at the End of Study Visit. The CFRSD responses will be entered into the eCRF by clinical site staff.

10 SAFETY ASSESSMENTS

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

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

10.1 Safety Monitoring Committee (SMC)

The SMC will provide safety oversight for the study. Several SMC members have significant experience with oversight of cystic fibrosis clinical trials, appointed by the Cystic Fibrosis Foundation Data Safety Monitoring Board. A SMC operational charter will be finalized prior to randomization of the first subject. The SMC will review blinded safety data from each cohort, and provide their recommendation for proceeding to the next dosing cohort, and for proceeding from the SAD phase to the MAD phase of the study, as described in Section 5.

10.2 Adverse Events

10.2.1 Definition

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. AEs can include any unfavorable, noxious, unintended sign, symptom, or disease temporally associated with use of an investigational medicinal product or other protocol-imposed intervention, regardless of attribution. AEs may be spontaneously reported by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory test, or other means.

AEs include:

- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period (as specified in Section 10.4.1)
- Complications that occur as a result of protocol-mandated interventions (e.g. invasive procedures such as blood draws)
- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g. invasive procedures such as blood draws, medication washout, or no treatment run-in)

10.3 Assessment of Adverse Events

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

10.3.1 Assessment of the Severity (Intensity) of Adverse Events

Maximum intensity is to be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (U.S. Department of Health and Human Services, 2017). If the CTCAE reference table does not include grading criteria for the event, the criteria in the table below will be used.

Table 8 Adverse Event Intensity (Severity) Scale

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

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

Any AE that meets the seriousness criteria (see Section 10.5, Serious Adverse Event Definition) will be considered an SAE, including all life-threatening AEs. In addition, AEs with Grade 4 intensity may be considered serious if the event is determined to be clinically significant.

10.3.2 Assessment of the Relationship of Adverse Events to Study Drug

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

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

Possibly Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition,

other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

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

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

10.3.3 Assessment of the Outcome of Adverse Events

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

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

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

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

Fatal: The death is related to the event.

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

10.4 Reporting of Adverse Events

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

10.4.1 Adverse Event Reporting Period

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

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

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

10.4.2 Eliciting Adverse Events

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

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

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

10.4.3 Recording Adverse and Serious Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the CRF and/or SAE form. Colloquialisms and abbreviations should be avoided. SAEs must also be recorded on the AE CRF. Only one medical concept should be recorded in the event field on the AE CRF and SAE form (if applicable).

a. Signs and Symptoms versus Diagnosis

Signs and symptoms should be recorded on the AE CRF rather than the unifying diagnosis. The unifying event term or diagnosis should be recorded as the "etiology" in the CRF (if known), and the SAE form, if applicable. For example, jaundice, asterixis, and elevated transaminases should be recorded on the CRF, and "liver failure" should be recorded as the etiology. As another example, cough, rhinitis, and sneezing should be recorded as AEs on the

CRF, and record "upper respiratory tract infection" as the etiology. Vague, nonspecific AE terms such as "erythema," "rash," or "lump on head" should be avoided and more specific information should be provided, such as "erythematous macule on right leg." "allergic dermatitis," and "scalp cyst."

b. Adverse Events Occurring Secondary to Other Events

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

c. Persistent or Recurrent Adverse Events

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

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

d. Abnormal Laboratory Values

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

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

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

e. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 10.4.1), regardless of attribution, will be recorded on the AE CRF and SAE form and reported to the Sponsor within 24 hours of event knowledge.

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

f. Preexisting Medical Conditions

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

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

g. Pulmonary Exacerbation

Given the proposed mechanism of action of AP-PA02, it could be anticipated that subjects will experience a change in baseline cough, change in sputum quality, or change in sputum volume. A diagnosis of pulmonary exacerbation should be considered if these symptoms are accompanied by fever, body weight loss, and/or generalized malaise. COVID-19 disease or other infections should also be strongly considered and evaluated by testing at the discretion of the treating physician. If a pulmonary exacerbation is diagnosed, appropriate interventions including additional antibiotics should be prescribed by the Investigator or treating physician. Subjects diagnosed with a pulmonary exacerbation requiring the addition of antibiotics will be discontinued from study drug, but will continue to be followed for safety through the End of Study visit.

h. Hospitalization, Prolonged Hospitalization or Surgery

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

i. Pregnancy

Abortion, whether therapeutic, or spontaneous, will be reported on a Pregnancy Report form and faxed to the Sponsor according to the instructions in the Study Manual. If the abortion meets seriousness criteria (see Section 10.5, Serious Adverse Event Definition), this information will be captured on the AE CRF and SAE form.

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

If a female subject becomes pregnant while still scheduled to receive additional study drug doses, study drug should be discontinued, and should remain in the study for safety follow-up through the End of Study Visit, in addition to the required pregnancy follow-up as described above.

If a female partner of a male study subject becomes pregnant while her partner is receiving study drug, or within 30 days following the last dose of study drug, a Partner Pregnancy Report form should be completed and submitted to the Sponsor's Drug Safety Department

(or designee) within 24 hours of learning of the pregnancy (see Study Manual for reporting instructions).

j. Overdose Reporting

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

10.5 Serious Adverse Events

10.5.1 Definition

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

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

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical

significance (such as severe headache). “Serious” is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject’s life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

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

10.6 Suspected Unexpected Serious Adverse Reaction Definition (SUSAR)

A SUSAR is a suspected unexpected serious adverse reaction. In order to be qualified as a SUSAR, the AE must meet 3 criteria: the event is serious, there is a certain degree of probability that the event is a reaction to the medical product being researched, and the nature and severity of the reaction are not in agreement with the product information (ie, the reaction is unexpected as per the reference safety information).

10.7 Serious Adverse Events Notification

For all SAEs, regardless of suspected causality, an SAE form must be completed (or faxed if using paper form) within 24 hours of discovery of the event. Instructions for the reporting of safety events are outlined in the Study Manual.

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

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

- If complete information is not available, at a minimum, subject identifier, suspect drug, site identifier, event or outcome, and Investigator assessment of causal relationship to study drug should be provided.
- A rationale for the causality assessment of an SAE should always be included, so that a better understanding of the event can be compiled.
- Follow-up information, such as laboratory reports, discharge summaries, autopsy reports, and information concerning outcome of the event should be submitted by revising the SAE form as soon as the information becomes available. Copies of source documents with subject identifiers redacted should be submitted only when they are written in English. If source documents are not in English, the Investigator must summarize the source documents, providing a complete English narrative that includes a description of the events as it evolved, the results of all diagnostic procedures performed, treatments administered, and outcome of the event. A query regarding a follow-up report should be answered within 5 working days from receipt of the query.

- Appropriate diagnostic tests and therapeutic measures are to be performed as necessary and reported on the SAE form.
- All SAEs must be reported to the IRB/IEC, if applicable. See ICH GCP E6(R2), Section 4.11.1.

10.8 Expedited Reporting of SUSARs

- The Sponsor or its designee is responsible for notifying the investigational sites of all expedited SAEs (ie, 7/15 Day SUSARs) that occur during any clinical studies that are using the investigative compound. The Sponsor or its designee shall also notify the Central IRB of SUSARs or significant risks to subjects, per FDA requirements.
- The Investigator will notify local IRB or Local Ethics Committees (LECs) of SUSARs or significant risks to subjects, per local country requirements. The Investigator must keep copies of all AE information, including correspondence with the Sponsor or Local Ethics Committees on file.
- The Sponsor will also notify FDA of SUSARs as per 21 CFR 312.32.

10.9 Emergency Unblinding Procedure

In the event of a medical emergency, when knowledge of treatment assignment is needed for immediate medical management of the subject's health, Investigators can obtain unblinded treatment assignment through the centralized Interactive Response Technology (IRT) system at any time. Thorough documentation of the rationale for unblinding is required. Consultation of the study Medical Monitor and/or Sponsor designee is recommended for all unblinding requests.

11 STATISTICAL METHODOLOGY

11.1 General Considerations

A comprehensive Statistical Analysis Plan (SAP) specifying the statistical methodology, and table, listing and figure (TLF) formats for all aspects of the planned analyses will be finalized prior to database lock. The SAP supports the completion of the Clinical Study Report (CSR) for this protocol. As the risk profile of AP-PA02 in humans is unknown and this is a first in human trial, all AEs will be considered in determining the safety profile of AP-PA02 unless obviously unrelated. As an early phase clinical study, exploratory analyses not necessarily identified in the SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses not identified in the SAP will be clearly identified in the CSR, in accordance with applicable Standard Operating Procedures (SOPs) of the Sponsor or designee.

11.2 Determination of Sample Size

This is a Phase 1b/2a safety study designed to evaluate the safety, tolerability and phage titers of AP-PA02. 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.

Eight subjects will be enrolled in the SAD portion of the study, with 4 subjects per cohort (3 AP-PA02 and 1 placebo). Approximately 24 subjects will be enrolled in the MAD portion of the study, with 4 subjects in Cohort 3 (3 AP-PA02 and 1 placebo) and 20 subjects in Cohort 4 (15 AP-PA02 and 5 placebo). The exact number of subjects enrolled is dependent on whether any dose level is to be expanded due to the occurrence of DLTs.

11.3 Randomization and Blinding

11.3.1 Randomization Procedures

Following successful screening, potential subjects will be randomized through a centralized IRT system into the current enrolling cohort. All sites will be capable of and expected to enroll all cohorts of the study. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for randomization. The IRT system will be used to assign dose level and treatment assignments to subjects, within the cohort type (SAD or MAD) currently open to enrollment.

11.3.2 Sentinel Subject Precautions

Within each SAD dosing cohort, subjects will be randomized 3:1, AP-PA02 to placebo. Due to the fact that there are four subjects per SAD cohort, at least one of the first two subjects enrolled in each cohort will be randomized to receive AP-PA02. The first two subjects enrolled into the same SAD cohort will not be permitted to dose on the same day, to allow for adequate review of safety by the study Medical Monitor and/or Sponsor designee following dosing, as reported by the Investigator. If there are no significant findings for the

first two subjects following their dosing, as reported by the Investigator(s), the remaining subjects of the cohort are permitted to undergo study drug dosing.

Within each MAD dosing cohort, subjects will be randomized 3:1, AP-PA02 to placebo. At least one of the first two subjects enrolled in each cohort will be randomized to receive AP-PA02. The first two subjects enrolled into the same MAD cohort will not be permitted to initiate study drug dosing (Day 1) on the same day, to allow for review of adequate safety by the study Medical Monitor and/or Sponsor designee following dosing as reported by the Investigator. If there are no significant safety findings for the first two subjects following their respective Dosing Day 1 as reported by the Investigator, the remaining subjects are permitted to initiate study drug dosing (Day 1).

11.3.3 Blinding Procedures

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

11.3.4 Replacement of Subjects

Subjects who discontinue from the study after randomization without receiving any treatment will be replaced. If a subject has received at least one dose of study drug but discontinues the trial before receiving the full course of treatment, an additional subject could be added to the same treatment/dose to maintain the sample size. Any data collected from subjects who discontinue prematurely will be included in analyses as applicable. The decision for replacement will be made by the Sponsor based on available data and perceived need for additional data.

12 ANALYSIS OF POPULATIONS

Due to its exploratory nature, the analyses for this study will be descriptive. Data from the two parts of the study (SAD and MAD) will be summarized separately unless otherwise noted. Data will be summarized by dose groups, and when appropriate, pooled across dose groups.

Summary statistics for continuous data will include the number of subjects with non-missing data, mean, standard deviation, minimum, maximum. Additional summary statistics for applicable phage titer parameters may include geometric mean, and geometric coefficient of variation. For categorical variables, summary statistics will include frequency and proportions. Additional summary statistics may be provided for some endpoints as specified in the SAP. All data will be listed by subject, dose level and visit, where appropriate.

Safety Population: the population for safety analyses will consist of all subjects who receive any AP-PA02 or placebo.

Exploratory Efficacy Population: the population for efficacy (clinical activity) analysis will consist of all subjects who receive any AP-PA02 or placebo with at least one baseline and one post baseline assessment for a specific efficacy endpoint.

Phage Distribution and Clearance Population: the population for phage distribution analyses will consist of all subjects who receive AP-PA02 and who have at least one detectable AP-PA02 concentration measurement in sputum, blood or urine samples.

12.1 Subject Disposition, Demographics and Baseline Disease Characteristics

Subject disposition will be summarized for the safety population by dose group.

The number and percentage of subjects who receive AP-PA02 will be tabulated by the number of doses and the AP-PA02 dose group.

Subject demographics and baseline characteristics will be summarized for each study part and dose group. Subject characteristics at baseline include age, sex, race, body weight, height, and BMI. Baseline disease characteristics include pulmonary function (percent predicted), CFRSD-CRISS, and CFQ-R Respiratory Symptoms Score. The baseline data is defined as the data most recently collected prior to the first dose.

12.2 Treatment Compliance

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

12.3 Safety Analyses

12.3.1 Treatment Emergent Adverse Events

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

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

12.3.2 Dose-Limiting Toxicities

DLTs will be summarized overall, and by study part and dose group, and severity. Individual subject listings will be provided for each DLT including severity and other descriptive information such as associated laboratory values and action taken.

12.3.3 Vital Signs

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

12.3.4 Laboratory Assessments

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

- Descriptive statistics of actual results and changes from baseline (number of subjects, mean, standard deviation, median, minimum, and maximum) for the continuous data and frequencies and percentages for the categorical data, for each assessment visit
- Potentially clinically significant lab abnormalities for hematology, chemistry and coagulation will be summarized by study part, dose group and assessment visit.
- If appropriate, by-subject line plots may be presented by lab parameter, study part and dose group, to allow for significant out of range values to be further identified.

12.3.5 Immunogenicity

For subjects with positive anti-AP-PA02 antibodies, the correlation between antibody titer and concentration of AP-PA02 in blood and sputum will be examined. Correlation between antibody titer and any treatment emergent AEs (TEAEs) will also be examined.

12.3.6 Other Safety Assessments

Other safety assessments, such as ECGs, spirometry, and physical examinations will be summarized and listed as specified in the SAP.

12.4 Phage Recovery Analyses

12.4.1 Phage Recovery Measurements

In case of SAE or early withdrawal, a blood draw for phage recovery will be collected at or near the time the subject reports the SAE, or at the time of withdrawal, if deemed required by the Investigator.

12.4.1.1 SAD Measurements

In the SAD portion of the study blood and sputum samples will be obtained from each subject for phage recovery analyses. Blood samples will be collected prior to study drug administration, at the time points specified in the Schedule of Assessments appendix (approximately 5 mL of blood for each sampling time).

12.4.1.2 MAD Measurements

In the MAD portion of the study, blood and sputum samples will be obtained from each subject for phage recovery analyses. Blood samples will be collected prior to first study drug administration, at the time points specified in the Schedule of Assessments appendix (approximately 5 mL of blood for each sampling time).

12.4.1.3 Urine Samples

Urine for phage recovery will be collected prior to first study drug administration, at the time points specified in the Schedule of Assessments appendix.

12.4.2 Phage Recovery Analysis Methods

To examine the phage recovery profile of inhaled administrations at the different dose levels of AP-PA02, the following parameters will be calculated if sufficient data are available for each dose:

- C_{max}: The maximum blood concentration will be taken directly from the data.
- t_{max}: Time to C_{max} will be taken directly from the data.

- $t_{½}$: The terminal elimination half-life will be estimated by non-linear regression analysis of the terminal elimination slope, if feasible.
- AUC_{0-t}: Area under the curve to the final sample with a concentration greater than lower limit of quantification (LLQ) will be calculated using the linear trapezoidal method.
- $AUC_{0-\infty}$: Area under the curve to infinity will be calculated based on the last observed concentration C_{last}(obs) and the terminal phase rate constant (λz) using formula: $AUC_{0-\infty}=AUC_{last}+C_{last}(obs)/\lambda z$, if feasible.
- CL/F: Blood clearance will be estimated using the formula: $CL = Dose/AUC_{0-\infty}$.

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

Blood concentration below LLQ prior to dose for the assay will be set to zero for the phage titer analysis. For other cases concentrations below LLQ will be set for non-informative missing. Exact procedure for imputation of data will be described in the SAP.

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

Drug concentrations will be summarized by nominal time point if 3 or more values are available. Descriptive statistics for phage titer parameters will be performed if the number of values to summarize is ≥ 3.

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

In the case there is not sufficient data available to perform non-parametric analyses of exposure, a model-based approach may be applied. In such case, the method of exposure quantification will be described in a modeling analysis plan separate from the SAP.

Correlation between concentrations in different matrices (blood, urine, sputum) and response (safety, efficacy) may be explored.

12.5 Efficacy Analyses

The clinical efficacy endpoints for the study will be summarized for subjects included in the specific efficacy evaluable population for the parameter, by study part and dose group.

Change in sputum density of *P. aeruginosa* from Baseline through approximately 14 days after the last study drug dose for the MAD will be summarized as a secondary endpoint.

Exploratory efficacy endpoints will include:

- Change in *P. aeruginosa* isolates' sensitivity to AP-PA02 and/or its individual components from Screening to approximately 14 days after the last study drug dose
- Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) from Day 1 pre-dose through end of study
- Changes in the Cystic Fibrosis Respiratory Symptom Diary (CFRSD) and Chronic Respiratory Infection Symptom Score (CRISS) from baseline through the end of the study

Observation value and change from baseline value will be summarized using descriptive statistics in exploratory endpoints and will be tabulated by study part and dose group.

Further to the above, change in FEV_1 from baseline through end of study will also be summarized descriptively by study part and dose group; however as the FEV_1 endpoints form part of the safety and tolerability criteria, to avoid duplication it will be presented as Safety analysis, under the Safety population. See Section 12.3.6 for further details.

12.6 Interim Analysis

Safety will be assessed prior to each dose escalation by the SMC, as described in Section 9.1. No formal interim analyses for efficacy or futility are planned.

An interim analysis for phage titer may be performed. Further details regarding the handling of any interim phage titer data and analyses will be described in the SAP. Only personnel involved in phage titer analyses will be granted access to the unblinded data before database lock. No formal interim report will be generated.

12.7 Subgroup Analyses

No subgroup analyses are planned.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Changes to the Protocol

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

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

13.2 Data Collection and Study Monitoring

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

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

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

To ensure the quality of clinical data across all subjects and sites, a clinical data management review will be performed on subject data. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries will be sent to the site. Corrections or updates to the data resulting from queries should be made on the eCRF. All changes will be automatically documented in the software's audit trail, including the reason for change.

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

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

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

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

14 ETHICAL AND REGULATORY OBLIGATIONS

14.1 Ethical Considerations

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

14.2 Informed Consent

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

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

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

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

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

14.3 Pre-Study Documentation Requirements

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

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

14.4 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

14.5 Subject Confidentiality

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

In compliance with federal and local regulations, it is required that the Investigator and institution permit authorized representatives of the Sponsor, the Food and Drug Administration, other regulatory authorities, and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any or all records

and reports that are important to the evaluation of this study. The Investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to the study-related records without violating the confidentiality of the subject.

14.6 Dissemination of Clinical Study Data

The Sponsor is responsible for posting appropriate study information on applicable websites including the US National Institutes of Health's website www.clinicaltrials.gov. Information included in clinical study registries may include participating investigators' names and contact information.

15 STUDY ADMINISTRATION

15.1 Good Clinical Practice and Regulatory Requirements

This study will be conducted in accordance with good clinical practices as described in the ICH E6(R2) GCP, adopted 9 November 2016, and in accordance with CFR Parts 50, 56, 312, and 314. The ICH guideline may be obtained at the ICH web site:

https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

15.2 Investigator's Brochure

Before the study begins, the Investigator will receive the AP-PA02 Investigator's Brochure describing all known contraindications, warnings, precautions, and adverse reactions associated with the administration of the study drug. If such information is revised while the study is in progress, the brochure will be amended or revised, and the Sponsor will provide the most current version to the Investigator.

15.3 Protocol Amendments and Study Termination

Protocol amendments must be made only with the prior approval of Sponsor. Sponsor will inform the Investigator in writing of any amendment to the protocol. The Investigator must submit the protocol modifications and any informed consent modifications to the IRB/IEC, and approval must be obtained before the modifications are implemented. The Investigator must send a copy of the approval letter from the IRB/IEC to the CRO for Sponsor to review.

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

15.4 Study Documentation and Storage

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

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

In addition, all original source documents supporting entries in the CRFs/eCRFs must be maintained and be readily available for inspection. Upon the request of the Sponsor, designees, or the regulatory authorities, the Investigator will make any and all study records available for inspection, including subject dairies and source documents. This information will be treated as confidential.

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

15.5 Use of Information

All personal information pertaining to the subjects in this study and in any subsequent reports will be kept confidential. Subjects will be identified only by their month and year of birth and a unique, anonymized subject number. It is the responsibility of the Investigator to keep a subject listing for cross-referencing and subject contact information in case of an emergency.

The Investigator understands that the information developed in the clinical study will be used by the Sponsor in connection with the development of the study drug. This information may be disclosed to other clinical Investigators, to the U.S. FDA, and to other government agencies.

15.6 End of Trial and Final Report

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

15.7 Financing and Insurance

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

15.8 Publication Policy

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

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17 APPENDICES

APPENDIX 1 SCHEDULE OF ASSESSMENTS

Table A: Schedule of Procedures Part 1 SAD Cohorts 1 and 2

Study Visit	**Scr**	**BL**	**1**[1]	**2**	**3**[2]	**4**	**5**	**6 EOS**
Nominal Study Day:	–35 to –2	-7 to -1	1	2	3	8	15	29
Visit Window (±days)			-	-	+ 3	±3	±3	±3
Informed Consent Form	X							
Demographics / Medical History	X							
Eligibility Criteria	X	X	X					
Administer CFQ-R			X				X	X
Randomization		X						
Study Drug Administration			X					
Concomitant Medications Review	X	X	X	X	X	X	X	X
Adverse Events Assessment		X	X	X	X	X	X	X
Physical Examination[3]	Full	Full	SD	SD	SD	SD	Full	SD
Height and Weight	H/W	W					W	W
Vital Sign Measurements & Oximetry (Temp, BP, RR, HR, SpO_2)[4]	X	X	X	X	X	X	X	X
Spirometry (FEV_1, FVC, FEF_{25-75})[5]	X	X	X[1]	X	X	X	X	X
12-lead ECG	X		X[1]					
CFTR Genotyping or Sweat Chloride[6]	X							
Pregnancy Test for females of childbearing potential	X	X						X
Daily Symptom Diary (CFRSD)		dispense	review	review	review	review	review	collect

[1] Close safety monitoring will be performed on Day 1 pre and post dose at the following timepoints (refer to Table B regarding safety monitoring timepoints and sample collection on Day 1): Vital signs and oximetry will be measured at 10, 30 and 60 minutes, and at 2, 4, and 7 hours post dose; 12-lead ECG at 60 minutes post dose; spirometry at 30 minutes, 60 minutes and 7 hours post dose.
[2] Study Visit 3 = 48-144 hours post first dose
[3] Physical Exam: Full exams performed at Screening, Baseline (BL) and Day 15. Symptom-directed (SD) exams performed at all other visits.
[4] Vital signs: Oral Body Temperature (Temp), Blood Pressure (BP), Respiratory Rate (RR), Heart Rate (HR), Oxygen saturation by digital oximetry (SpO_2)
[5] Spirometry to be performed prior to sputum induction at Screening, BL, and Visits 4 and 5
[6] If no historical CFTR genotyping or sweat chloride result available

Table A: Schedule of Procedures Part 1 SAD Cohorts 1 and 2								
Study Visit	**Scr**	**BL**	**1**[1]	**2**	**3**[2]	**4**	**5**	**6 EOS**
Nominal Study Day:	–35 to –2	-7 to -1	1	2	3	8	15	29
Visit Window (±days)			-	-	+ 3	±3	±3	±3
Safety Labs Sample Collection[7]**:**								
Blood for Hematology/Chemistries	X	X		X	X	X	X	
Blood for Coagulation	X							
Urine for Urinalysis	X	X		X			X	
Sputum for Microbiology:								
Induced Sputum Sample Required[8]	*	*	*	*	*		*	
Quantitative Culture of *P. aeruginosa*	X	X		X	X		X	
Antipseudomonal Antibiotic Sensitivity of *Pa* Isolates	X	X					X	
Phage Sensitivity of *Pa* Isolates	X						X	
Expectorated Sputum Sample[9]			*	*	*	*		
Sputum for Quantitative Culture of *P. aeruginosa*			X[10]	X	X	X		
Phage Titer/ADA Sampling[11]**:**								
Blood for phage titer		X	X	X				
Sputum for phage titer[12]		X	X	X	X	X	X	
Serum for AP-PA02 ADA & SARS-CoV2		X					X	X
Urine samples for phage clearance		X		X			X	

[7] Samples for clinical lab testing to be analyzed at the site local laboratory
[8] Sputum induction to be performed LAST at Screening, BL, Visits 2, 3 and 5
[9] Expectorated sputum samples to be collected by the subject at home prior to the study visit are requested in addition to the samples collected in the clinic, for subjects who are able to expectorate.
[10] For subjects who are able to expectorate, sample to be obtained pre-dose on Day 1. Sample may be collected by the subject at home prior to the study visit or collected in the clinic.
[11] See Appendix Table B for various timepoints for sample collection on Day 1
[12] Performed on induced and expectorated sputum sample (if available) (performed at central laboratory). Samples for phage titer to be transported in separate collection vessels for each time point and collection method.

Table B: Timing of Sample Collection and Procedures on Day 1 for SAD Cohorts										
Test/Procedure	**Pre-Dose**	**Dose Admin**	**Nominal Time Post Dose**							
		Time 0	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**	**2 hr**	**4 hr**	**7 hr**
Study Drug Administration		X								
Spirometry	X				X		X[13]			X
Vital Signs & Oximetry	X		X		X		X	X	X	X
12-lead ECG	X						X			
Blood & Urine for Safety Labs[14]	X									
Sputum for Microbiology:										
Expectorated Sputum for Quantitative Culture of *P. aeruginosa*	X[15]									
Phage Titer/ADA Sampling										
Blood for Phage Titer				X		X		X		X
Induced Sputum for Phage Titer								X[16]		
Expectorated Sputum for Phage Titer[17]	X		X[18]						X[19]	

[13] Spirometry to be measured after vital signs/oximetry and 12-lead ECG assessments
[14] Samples for clinical lab testing obtained pre-dose on Day 1, if abnormal and clinically significant at Baseline (BL) and results reviewed by Investigator prior to administration of study drug; To be analyzed at the site local laboratory
[15] For subjects who are able to expectorate, sample to be obtained pre-dose on Day 1. Sample may be collected by the subject at home on Day 1 prior to the study visit or collected in the clinic.
[16] Induced sputum to be collected after vital signs/oximetry measurements and blood collection at the 2 hour time point
[17] Expectorated sputum for phage titer to be obtained as able post-dose on Day 1, performed at central laboratory (above are desired nominal timeframes when sputum samples are to be collected. Actual collection times to be recorded in eCRF).
[18] If able to expectorate; optimal sample collection timeframe up to 1 hour post dose
[19] If able to expectorate; optimal sample collection timeframe between 4 and up to approximately 7 hours post dose

Schedule of Procedures Part 2 MAD Cohort 3 (5 Days of Dosing)

Table C: Schedule of Procedures Part 2 MAD Cohort 3 (5 Days of Dosing)											
Study Visit	Scr	BL	1	2	3	4	5 EOT	6	7	8	9 EOS
Nominal Study Day	–35 to –2	-7 to -1	1	2	3	4	5	6	12	19	33
Visit Window (±days)			-	-	-	-	-	+ 3	± 3	± 3	± 3
Informed Consent Form	X										
Demographics / Medical History	X										
Eligibility Criteria	X	X	X								
Administer CFQ-R			X						X	X	X
Pregnancy test for females of childbearing potential	X	X									X
Randomization		X									
Study Drug Administration[20]			X	X	X	X	X				
Concomitant Medications Review	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Assessment[21]		X	X	X	X	X	X	X	X	X	X
Physical Examination[22]	Full	Full	SD	SD	SD	SD	SD	SD	SD	SD	Full
Height and Weight	H/W	W									W
Vital Sign measurements & oximetry (Temp, BP, RR, HR, SpO_2)[23]	X	X	X	X	X	X	X	X	X	X	X
Spirometry (FEV_1, FVC, FEF_{25-75})[24]	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X		X[25]								X
CFTR Genotyping or Sweat Chloride[26]	X										
Daily Symptom Diary (CFRSD)		dispense	review	review	review	review	review	review	review	review	collect

[20] Study drug to be administered twice per day, at least 6 hours apart.
[21] Close safety monitoring will be performed on Dosing Days 1-5 pre and post dose (refer to Tables D and E regarding safety monitoring timepoints and sample collection on dosing days).
[22] Physical Exam: Full exams performed at Screening, Baseline (BL), and EOS. Symptom-directed (SD) exams performed at all other visits.
[23] Vital signs: Oral Body Temperature (Temp), Blood Pressure (BP), Respiratory Rate (RR), Heart Rate (HR), Oxygen saturation by digital oximetry (SpO_2)
[24] Spirometry to be performed prior to sputum induction at designated visits; Spirometry on dosing days to performed as detailed on Tables D and E
[25] Day 1 12-lead ECG prior to drug administration and 1 hour post dose
[26] If no historical CFTR genotyping or sweat chloride value available

Table C: Schedule of Procedures Part 2 MAD Cohort 3 (5 Days of Dosing)											
Study Visit	Scr	BL	1	2	3	4	5 EOT	6	7	8	9 EOS
Nominal Study Day	–35 to –2	-7 to -1	1	2	3	4	5	6	12	19	33
Visit Window (±days)			-	-	-	-	-	+ 3	± 3	± 3	± 3
Safety Labs Sample Collection[27]:											
Blood for Hematology/Chemistries	X	X		X			X		X	X	
Blood for Coagulation	X										
Urine for Urinalysis	X	X						X		X	
Sputum for Microbiology:											
Induced Sputum Sample Required [28]	*	*	*	*	*	*	*	*	*	*	*
Quantitative Culture of *P. aeruginosa*	X	X			X	X	X	X	X	X	X
Antipseudomonal Antibiotic Sensitivity of *Pa* Isolates	X	X								X	
Phage Sensitivity of *Pa* Isolates	X									X	
Expectorated Sputum Sample[29]			*	*	*	*	*				*
Quantitative Culture of *P. aeruginosa*			X[30]		X	X	X				
Phage Titer[31, 32] / ADA Sampling:											
Blood for Phage Titer		X	X	X	X	X	X	X	X	X	X
Sputum for Phage Titer[33]		X	X	X	X	X	X	X	X	X	X
Serum for AP-PA02 ADA & SARS-CoV2		X								X	X
Urine Samples for Phage Clearance		X						X		X	

[27] Samples for clinical lab testing obtained pre-dose on designated dosing days; Safety lab results from the prior visit to be reviewed as available by Investigator prior to administering the next dose of study drug; To be analyzed at the site local laboratory.
[28] Sputum induction to be performed LAST at Screening, BL, Visits 1, 5, and 6-9 (non-dosing days); Visits 2-4 to be performed pre-first dose of the day.
[29] Expectorated sputum samples to be collected by the subject at home prior to the study visits indicated are requested in addition to the sample collected in the clinic, for subjects who are able to expectorate.
[30] For subjects who are able to expectorate, sample to be obtained pre-dose on Day 1. Sample may be collected by the subject at home on Day 1 prior to the study visit or collected in the clinic.
[31] If phage titer signal detected from samples obtained at End of Study Visit, subjects may be requested to provide additional samples until titer is no longer detectable
[32] See Appendix Table D for various timepoints for sample collection on Day 1. Samples for phage titers to be transported in separate collection vessels for each time point and collection method.
[33] Pre-dose on dosing days 2-4

Table D: Timing of Sample Collection and Procedures on Day 1 for MAD Cohort 3											
Test/Procedure	**Pre-Dose**	**Nominal Times Post First Dose**									
		Time 0	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**	**2 hr**	**5 hr**	**6 hr**	**7 hr**
Study Drug Administration		X								X	
Spirometry	X				X			X			X
Vital Signs & Oximetry[34]	X		X				X			X	X
12-lead ECG	X						X				
Blood & Urine for Safety Labs[35]	X										
Sputum for Microbiology:											
Expectorated Sputum for Quantitative Culture of *P. aeruginosa*	X[36]										
Phage Titer/ADA Sampling											
Blood for Phage Titer				X		X		X	X		X
Induced Sputum for Phage Titer											X[37]
Expectorated Sputum for Phage Titer[38]			X[39]					X[40]	X[41]		

[34] Vital signs and oximetry to be measured pre-dose, and at the other designated time points post-first dose of the day
[35] Samples for clinical lab testing obtained pre-first dose on Day 1 if abnormal and clinically significant at Baseline (BL), and results reviewed by Investigator prior to administration of study drug; To be analyzed at the site local laboratory.
[36] For subjects who are able to expectorate, sample to be obtained pre-dose on Day 1. Sample may be collected by the subject at home in the morning just prior to the study visit or collected in the clinic.
[37] Sputum induction to be performed LAST at the timepoint indicated
[38] Expectorated sputum for phage titer to be obtained as able post-dose on Day 1, performed at central laboratory (above are desired nominal timeframes when sputum samples are to be collected. Actual collection times to be recorded in eCRF.)
[39] If able to expectorate; optimal sample collection timeframe up to 1 hour post Dose 1
[40] If able to expectorate; optimal sample collection timeframe between 2 and 4 hours post Dose 1 (single spot sample, not cumulative during this time period)
[41] If able to expectorate; optimal sample collection timeframe within 1 hour prior to Dose 2 (single spot sample, do not combine with 2-4 hour sample)

Table E: Timing of Sample Collection and Procedures on Dosing Days 2 through Day 5 for MAD Cohort 3											
Test/Procedure	**Pre-First Dose**	**Nominal Times Post First Dose**									
		Time 0	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**	**2 hr**	**5 hr**	**6 hr**	**7 hr**
Study Drug Administration		X								X	
Spirometry	X				X						X
Vital Signs & Oximetry[42]	X		X				X			X	X
Blood for Safety Labs[43]	X										
Phage Titer											
Blood for Phage Titer	X			X[44]		X[44]		X[44]	X[44]		X[44]
Expectorated Sputum for Phage Titer	X[45]							X[46]	X[47]		
Induced Sputum for Phage Titer	X[48]										X[49]

[42] Vital signs and oximetry to be measured prior to each dose on Days 2 through 5, and at the other designated time points post-first dose of the day
[43] Samples for clinical lab testing obtained pre-first dose on Days 2 and 5 only; Safety labs results from the prior visit to be reviewed as available by Investigator prior to administration of study drug; To be analyzed at the site local laboratory.
[44] Blood for phage titer to be obtained on Day 5 only.
[45] Expectorated sputum for phage titer to be obtained as able pre-first dose on Days 2 through 5. Sample to be collected by the subject at home in the morning just prior to the study visit or in the clinic (if the subject is able to expectorate).
[46] If able to expectorate; optimal sample collection timeframe up to 2 hours post Dose 1 of the day (single spot sample do not combine with 2–4-hour sample).
[47] If able to expectorate; optimal sample collection timeframe between 2 and 4 hours post Dose 1 of the day (single spot sample do not combine during this period).
[48] Induced sputum for phage titer to be obtained pre-first dose on Days 2, 3 and 4.
[49] Induced sputum for phage titer to be obtained last on Day 5 only.

Schedule of Procedures Part 2 MAD Cohort 4 (10 Days of Dosing)

Table F: Schedule of Procedures Part 2 MAD Cohort 4 (10 Days of Dosing)																
Study Visit	Scr	BL	1	2	3	4	5	6	7	8	9	10 EOT	11	12	13	14 EOS
Nominal Study Day	–35 to –2	-7 to -1	1	2	3	4	5	6	7	8	9	10	11	17	24	38
Visit Window (±days)			-	-	-	-	-							± 3	± 3	± 3
Informed Consent Form	X															
Demo / Medical History	X															
Eligibility Criteria	X	X	X													
Administer CFQ-R			X											X	X	X
Pregnancy test for females of childbearing potential	X	X														X
Randomization		X														
Study Drug Admin[50]			X	X	X	X	X	X	X	X	X	X				
Concomitant Meds Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Assessment[51]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[52]	Full	Full	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	FULL
Height and Weight	H/W	W														W
Vital Signs & Oximetry [53]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry (FEV_1, FVC, FEF_{25-75})[54]	X	X	X	X	X	X				X	X	X	X	X	X	X
12-Lead ECG	X		X[55]													X
CFTR Genotyping or Sweat Chloride[56]	X															
Daily Symptom Diary (CFRSD)[57]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[50] Study drug to be administered twice per day, at least 6 hours apart.
[51] Close safety monitoring will be performed on Dosing Days 1-10 pre and post dose (refer to Tables G, H and I regarding safety monitoring timepoints and sample collection on dosing days).
[52] Physical Exam: Full exams performed at Screening, Baseline (BL), and EOS. Symptom-directed (SD) exams performed at all other visits.
[53] Vital signs: Oral Body Temperature (Temp), Blood Pressure (BP), Respiratory Rate (RR), Heart Rate (HR), Oxygen saturation by digital oximetry (SpO_2)
[54] Spirometry to be performed prior to sputum induction at designated visits; Spirometry on dosing days to performed as detailed on Tables G and H
[55] Day 1 12-lead ECG prior to drug administration and 1 hour post dose
[56] If no historical CFTR genotyping or sweat chloride value available
[57] Dispense at BL, collect and review at each visit

Table F: Schedule of Procedures Part 2 MAD Cohort 4 (10 Days of Dosing)																
Study Visit	Scr	BL	1	2	3	4	5	6	7	8	9	10 EOT	11	12	13	14 EOS
Nominal Study Day	–35 to –2	-7 to -1	1	2	3	4	5	6	7	8	9	10	11	17	24	38
Visit Window (±days)			-	-	-	-	-							± 3	± 3	± 3
Safety Labs Collection[58]:																
Blood for Hem/Chem	X	X		X								X		X	X	
Blood for Coag	X															
Urine for Urinalysis	X	X										X			X	
Sputum for Microbiology:																
Induced Sputum Required [59]	*	*	*	*	*	*				*	*	*	*	*	*	*
Quant Culture of *Pa*	X	X			X	X				X	X	X	X	X	X	X
Anti *Pa* Abx Sensitivity of *Pa* Isolates	X	X													X	X
Phage Sensitivity of *Pa*	X														X	X
Expectorated Sputum [60]			*	*	*	*				*	*	*				
Quant Culture of *Pa*			X[61]	X	X	X				X	X	X				
Phage Titer[62, 63] / ADA:		X													X	X
Blood for Phage Titer		X	X	X	X	X				X	X	X	X	X	X	X
Sputum for Phage Titer[64]		X	X	X	X	X				X	X	X	X	X	X	X
Serum for AP-PA02 ADA & SARS-CoV2		X													X	X
Urine Samples for Phage Clearance		X											X		X	

[58] Samples for clinical lab testing obtained pre-dose on designated dosing days; Safety lab results from the prior visit to be reviewed as available by Investigator prior to administering the next dose of study drug; To be analyzed at the site local laboratory.
[59] Sputum induction to be performed LAST at Screening, BL, Visits 1, 10, and 11-14 (non-dosing days); Sputum induction to be performed pre-first dose of the day at Visits 2-4, 8-9.
[60] Expectorated sputum samples to be collected by the subject at home prior to the study visits indicated are requested in addition to the sample collected in the clinic, for subjects who are able to expectorate.
[61] For subjects who are able to expectorate, sample to be obtained pre-dose on Day 1. Sample may be collected by the subject at home on Day 1 prior to the study visit or collected in the clinic.
[62] If phage titer signal detected from samples obtained at End of Study Visit, subjects may be requested to provide additional samples until titer is no longer detectable.
[63] See Appendix Tables G and H for various timepoints for sample collection on dosing days. Samples for phage titers to be transported in separate collection vessels for each time point and collection method.
[64] Pre-dose on dosing days 2-4, 8-9

Table G: Timing of Sample Collection and Procedures on Day 1 for MAD Cohort 4											
Test/Procedure	**Pre-Dose**	**Nominal Times Post First Dose**									
		Time 0	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**	**2 hr**	**5 hr**	**6 hr**	**7 hr**
Study Drug Administration		X								X	
Spirometry	X				X			X			X
Vital Signs & Oximetry[65]	X		X				X			X	X
12-lead ECG	X						X				
Blood & Urine for Safety Labs[66]	X										
Sputum for Microbiology:											
Expectorated Sputum for Quant Culture of *Pa*	X[67]										
Phage Titer/ADA Sampling											
Blood for Phage Titer				X		X		X	X		X
Induced Sputum for Phage Titer											X[68]
Expectorated Sputum for Phage Titer[69]			X[70]					X[71]	X[72]		

[65] Vital signs and oximetry to be measured pre-dose at the designated time points post-first dose of the day
[66] Samples for clinical lab testing obtained pre-first dose on Day 1 if abnormal and clinically significant at Baseline (BL) and results reviewed by Investigator prior to administration of study drug; To be analyzed at the site local laboratory.
[67] For subjects who are able to expectorate, sample to be obtained pre-dose on Day 1. Sample may be collected by the subject at home prior to the study visit or collected in the clinic.
[68] Sputum induction to be performed LAST at the timepoint indicated
[69] For subjects who are able to expectorate, expectorated sputum for phage titer to be obtained as able post-dose on Day 1, performed at central laboratory (above are desired nominal timeframes when sputum samples are to be collected. Actual collection times to be recorded in eCRF.)
[70] If able to expectorate; optimal sample collection timeframe up to 1 hour post Dose 1
[71] If able to expectorate; optimal sample collection timeframe between 2 and 4 hours post Dose 1 (single spot sample, not cumulative during this time period)
[72] If able to expectorate; optimal sample collection timeframe within 1 hour prior to Dose 2 (single spot sample, do not combine with 2-4 hour sample)

Table H: Timing of Sample Collection and Procedures on Dosing Days 2-4 and 8-10 for MAD Cohort 4											
Test/Procedure	**Pre- First Dose**	**Nominal Times Post First Dose**									
		Time 0	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**	**2 hr**	**5 hr**	**6 hr**	**7 hr**
Study Drug Administration		X								X	
Spirometry	X				X						X
Vital Signs & Oximetry[73]	X						X			X	X
Blood for Safety Labs[74]	X										
Phage Titer											
Blood for Phage Titer	X			X[75]		X[75]		X[75]		X[75]	X[75]
Expectorated Sputum for Phage Titer	X[76]							X[77]	X[78]		
Induced Sputum for Phage Titer	X[79]										X[80]

Table I: Timing of Sample Collection and Procedures on Dosing Days 5-7 for MAD Cohort 4											
Test/Procedure	**Pre- First Dose**	**Nominal Times Post First Dose**									
		Time 0	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**	**2 hr**	**5 hr**	**6 hr**	**7 hr**
Study Drug Administration		X								X	
Vital Signs & Oximetry[81]	X						X			X	X

[73] Vital signs and oximetry to be measured prior to each dose on Days 2-4 and 8-10, and at the designated time points post-first dose of the day.
[74] Samples for clinical lab testing obtained pre-first dose on Days 2 and 10 only; Safety labs results from the prior visit to be reviewed as available by Investigator prior to administration of study drug; To be analyzed at the site local laboratory.
[75] Blood for phage titer to be obtained on Day 10 only.
[76] Expectorated sputum for phage titer to be obtained as able pre-first dose on Days 2-4 and 8-10. Sample to be collected by the subject at home the morning just prior to the study visit (if the subject is able to expectorate).
[77] If able to expectorate; optimal sample collection timeframe up to 2 hours post-first dose of the day (single spot sample do not combine with 2–4-hour sample).
[78] If able to expectorate; optimal sample collection timeframe between 2 and 4 hours post-first dose of the day (single spot sample, not cumulative during this time period).
[79] Induced sputum for phage titer to be obtained pre-first dose on Days 2, 3, 4, 8, and 9.
[80] Induced sputum for phage titer to be obtained last on Day 10 only.
[81] Vital signs and oximetry to be measured pre each dose, and 60 minutes post each dose on Days 5-7.

APPENDIX 2 ADULT CFQ-R (ENGLISH)

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

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

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

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

Section I. Demographics

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

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

B. What is your gender?
☐ Male ☐ Female

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

☐ Yes ☐ No

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

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

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

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

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

Section II. Quality of Life

Please check the box indicating your answer.

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

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

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

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

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

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

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

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

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

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

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

Please select a box indicating your answer.

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

Cystic Fibrosis Foundation Page 3

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

Section III. School, Work, or Daily Activities

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

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

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

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

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

Section IV. Symptom Difficulties

Please select a box indicating your answer.

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

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

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

Please be sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

Cystic Fibrosis Foundation Page 4

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

Section III. School, Work, or Daily Activities

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

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

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

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

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

Section IV. Symptom Difficulties

Please select a box indicating your answer.

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

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

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

Please be sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

APPENDIX 3 CFRSD-CRISS

Cystic Fibrosis Respiratory Symptom Diary – (CFRSD©)

Self-Report – Version 2.0

Daily Recall

University Of Washington

Seattle Quality of Life Group and Department of Medicine

This work has been supported with a grant from the Cystic Fibrosis Foundation

Date										Participant's Initials			Participant ID#							
DD		MMM			YYYY					FIRST	MIDDLE	LAST				-				

Cystic Fibrosis: Your Daily Experience

Instructions:

- Complete this diary between 5:00 P.M. and when you go to bed each evening.
- Think carefully about **your experience with cystic fibrosis, specifically during the last 24 hours**, before responding to each question. The "last 24 hours" is the amount of time that has passed since the same time the previous day.
- ***Please complete all of the questions in one sitting if possible.***

What is today's date? *(write-in your answer)*:	_____, _____ 20____ MONTH DAY YEAR
What is the current time? *(write-in your answer, and circle "AM" (before noon) or "PM" (after noon):*	_____:_____ o' clock AM PM

Date								
DD		MMM			YYYY			

Participant's Initials		
FIRST	MIDDLE	LAST

Participant ID#						
			-			

During the last 24 hours…

1. How difficult was it to breathe? *(Check one)*

- Not difficult ☐
- A little difficult ☐
- Somewhat difficult ☐
- A good deal difficult ☐
- A great deal difficult ☐

During the last 24 hours…

2. How feverish did you feel (have a temperature)? *(Check one)*

- Not feverish ☐
- A little feverish ☐
- Somewhat feverish ☐
- A good deal feverish ☐
- A great deal feverish ☐

During the last 24 hours…

3. How tired did you feel? *(Check one)*

- Not tired ☐
- A little tired ☐
- Somewhat tired ☐
- A good deal tired ☐
- A great deal tired ☐

During the last 24 hours…

4. How bad were your chills or sweats? *(Check one)*

- No chills or sweats ☐
- Slightly Bad ☐
- Moderately Bad ☐
- Very Bad ☐
- Extremely Bad ☐

Please continue to the next page.

Date										Participant's Initials			Participant ID#							
DD		MMM			YYYY					FIRST	MIDDLE	LAST				-				

During the last 24 hours…

5. How bad was your cough? *(Check one)*

- No cough ☐
- Slightly Bad ☐
- Moderately Bad ☐
- Very Bad ☐
- Extremely Bad ☐

During the last 24 hours…

6. How much mucus did you cough up? *(Check one)*

- No mucus ☐
- A little mucus ☐
- Some mucus ☐
- A good deal of mucus ☐
- A great deal of mucus ☐

During the last 24 hours…

7. How much tightness in the chest did you have? *(Check one)*

- No tightness ☐
- A little tightness ☐
- Some tightness ☐
- A good deal of tightness ☐
- A great deal of tightness ☐

During the last 24 hours…

8. How bad was your wheezing? *(Check one)*

- No wheezing ☐
- Slightly Bad ☐
- Moderately Bad ☐
- Very Bad ☐
- Extremely Bad ☐

Please continue to the next page.

Date								
DD		MMM			YYYY			

Participant's Initials		
FIRST	MIDDLE	LAST

Participant ID#						
			-			

During the last 24 hours…

9. How difficult was it to sleep? *(Check one)*

- Not difficult ☐
- A little difficult ☐
- Somewhat difficult ☐
- A good deal difficult ☐
- A great deal difficult ☐

During the last 24 hours…

10. How worried were you about your cystic fibrosis? *(Check one)*

- Not worried ☐
- A little worried ☐
- Somewhat worried ☐
- A good deal worried ☐
- A great deal worried ☐

During the last 24 hours…

11. How cranky did you feel? *(Check one)*

- Not cranky ☐
- A little cranky ☐
- Somewhat cranky ☐
- A good deal cranky ☐
- A great deal cranky ☐

During the last 24 hours…

12. How sad or depressed did you feel? *(Check one)*

- Not sad or depressed ☐
- A little sad or depressed ☐
- Somewhat sad or depressed ☐
- A good deal sad or depressed ☐
- A great deal sad or depressed ☐

Please continue to the next page.

Date								
DD		MMM			YYYY			

Participant's Initials		
FIRST	MIDDLE	LAST

Participant ID#						
			-			

During the last 24 hours…

13. How frustrated did you feel? *(Check one)*

- Not frustrated ☐
- A little frustrated ☐
- Somewhat frustrated ☐
- A good deal frustrated ☐
- A great deal frustrated ☐

During the last 24 hours…

14. How much time did you spend sitting or lying down? *(Check one)*

- Hardly any of the time ☐
- Some of the time ☐
- Most of the time ☐
- All of the time ☐

During the last 24 hours…

15. Did you reduce your usual activities? *(Check one)*

- Yes ☐
- No ☐

During the last 24 hours…

16. Did you miss work or school? *(Check one)*

- Yes ☐
- No ☐
- Does not apply, I did not have work or school in the last 24 hours ☐