NCT05616221

CLINICAL STUDY PROTOCOL

A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety, Phage Kinetics, and Efficacy of Inhaled AP-PA02 Multi-Phage Therapeutic in Subjects with Non-Cystic Fibrosis Bronchiectasis and Chronic Pulmonary *Pseudomonas aeruginosa* Infection

Investigational Product: Anti-*Pseudomonas aeruginosa* Phage Product (AP-PA02)
Protocol Number: AP-PA02-201
EudraCT Number: 2021-006733-19

Sponsor:
Armata Pharmaceuticals, Inc.
4503 Glencoe Avenue
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United States
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Version Number: 5.0
Date: 19 December 2023

SIGNATURE PAGE

STUDY TITLE: A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety, Phage Kinetics, and Efficacy of Inhaled AP-PA02 Multi-Phage Therapeutic in Subjects with Non-Cystic Fibrosis Bronchiectasis and Chronic Pulmonary *Pseudomonas aeruginosa* Infection

We, the undersigned, have read this Protocol and agree that it contains all necessary information required to conduct the study.

Signature _____ Date 19 Dec 2023

Deborah Birx, MD Chief Executive Officer
Armata Pharmaceuticals, Inc.

Mina Pastagia _____ 19Dec2023

Mina Pastagia, MD
Chief Medical Officer
Armata Pharmaceuticals, Inc.

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this Protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this Protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this Protocol and access to all information furnished by Armata Pharmaceuticals, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Armata Pharmaceuticals, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Armata Pharmaceuticals, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethics Committee Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety, Phage Kinetics, and Efficacy of Inhaled AP-PA02 Multi-Phage Therapeutic in Subjects with Non-Cystic Fibrosis Bronchiectasis and Chronic Pulmonary *Pseudomonas aeruginosa* Infection

PROTOCOL NUMBER: AP-PA02-201

INVESTIGATIONAL PRODUCT: Anti-*Pseudomonas aeruginosa* Phage Product (AP-PA02)

PHASE: 2

INDICATION: Management of non-cystic fibrosis bronchiectasis (NCFB) subjects with chronic respiratory infections associated with *P. aeruginosa*

OBJECTIVE:

The primary objective is to evaluate the efficacy, safety, and phage kinetics of multiple inhaled doses of AP-PA02 administered as monotherapy and administered in combination with inhaled antibiotics compared to placebo and inhaled antibiotics alone.

POPULATION:

Inclusion criteria

Subjects who meet all of the following criteria will be considered eligible for enrollment in the study:

1. Are able and willing to comply with the Protocol and provide signed informed consent prior to any study-specific procedures;
2. Are male or female ≥18 years old;
3. Have a body mass index of ≥16.5 kg/m^2;
4. Have findings consistent with bronchiectasis per computerized tomography (CT) (or high-resolution CT [HRCT]);

   Note: A CT or HRCT that demonstrates the above criterion is required during Screening or the Screening Period unless such an examination has been performed within the last 5 years and meets the above criterion.
5. Have microbiological evidence of pulmonary *P. aeruginosa* infection from a sputum sample within the last 24 months. Sputum cultures may be repeated on up to 3 occasions during the Screening Period to document *P. aeruginosa* presence if the initial sputum culture is negative;
6. Are willing and able to provide an induced sputum sample at Screening or during the Screening Period and at designated time points during the study and are willing and able to provide a spontaneously expectorated or induced sputum at all other time points;

7. Have $\geq 10^4$ colony-forming units of *P. aeruginosa* per gram of induced sputum obtained at Screening or during the Screening Period. Up to 3 specimens may be collected to meet this criterion;
8. Have forced expiratory volume (FEV_1) ≥35% of predicted normal for age, gender, race, and height (using Global Lung Function Initiative standards) at Screening (regardless of the timing of the most recent prior administration of short-acting bronchodilator) or during the Screening Period;
9. Have, at the Baseline Visit, stable lung function, as determined by the Investigator, provided that the FEV_1 at the Baseline Visit has not decreased by more than 10% compared to the FEV_1 measured at Screening or during the Screening Period;
10. Have no acute infection or exacerbation of primary disease, as determined by the Investigator, prior to randomization and first dose of study drug;
11. Are able to reproducibly perform spirometry per American Thoracic Society/European Respiratory Society Standards;
12. Have past experience administering inhaled antibiotics and/or feel comfortable administering inhaled antibiotics and/or have a caregiver that is comfortable administering inhaled antibiotics to the subject;
13. For Cohort A, have not received chronic inhaled antipseudomonal antibiotic regimen for at least 3 months prior to Visit 1. For Cohort B, have received chronic inhaled antipseudomonal antibiotic regimen for at least 3 months prior to Visit 1;
14. Are able to comply with study visits and study procedures as judged by the Investigator;
15. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test at the Baseline Visit, with results known prior to randomization and first dose of study drug, if a woman of childbearing potential;
16. Must agree to use a highly effective method of birth control (defined as those, alone or in combination, that result in a low failure rate [ie, less than 1% per year]) from Screening through 60 days following the last dose of study drug if female or female partner of male subjects, of childbearing potential; and
17. Must agree to use barrier contraception (ie, condoms) from Day 1 through 60 days following the last dose of study drug if male. Male subjects must refrain from donating sperm throughout the study and until 60 days after the last dose of study drug.

Exclusion criteria

Subjects who meet any of the following criteria will not be eligible for enrollment in the study:

1. Have previously received 1 or more doses of AP-PA02 in any context, including, but not limited to, prior participation in study AP-PA02-101, prior enrollment in this study, or emergency use (with or without prior authorization);
2. Have a history of lung transplantation;
3. Have a history of primary or acquired immunodeficiency syndromes, including, but not limited to, hypogammaglobulinemia and common variable immunodeficiency;

4. Have a history of cystic fibrosis;
5. Have a history of α1-antitrypsin deficiency;
6. Have a history of pulmonary malignancy (primary or metastatic) or any other malignancy requiring treatment (including, but not limited to, chemotherapy, radiation therapy, or immunotherapy) within 1 year prior to Screening or anticipated during the study period (Exceptions: Basal cell carcinoma of the skin and carcinoma in situ of the cervix surgically excised and assessed as definitely removed);
7. Have, at Screening or during the Screening Period, either of the following findings:
   - A personal history or subject-reported family history of prolonged QT syndrome; or
   - Severe cardiovascular disease such as severe uncontrolled hypertension, unstable ischemic heart disease or cardiac arrhythmia and any other cardiac conditions that would confound the evaluation of safety in the opinion of the Investigator.
8. Have a history of hemoptysis meeting either of the following criteria:
   - Within the 6 months prior to Screening, was hospitalized for management or evaluation of hemoptysis; or
   - Within the 3 months prior to Screening, had hemoptysis totaling greater than 30 mL in a single day.
9. Have, within the 3 months prior to Screening, used supplemental oxygen during the day while at rest;
10. Have, within the 3 months prior to Screening, lost more than 10% of their body weight;
11. Have, within the 2 months prior to Screening, participated in any clinical study involving an investigational drug, an investigational device, or any systemic antibiotic;

    Note: For systemic drugs or antibiotics with a half-life >12 days, the exclusion period is 5 half-lives.
12. Have, within the 30 days prior to Screening, received any intravenous, intramuscular, or oral antipseudomonal antibiotic (Exception: Chronic oral macrolide treatment with a stable dose is permitted);

    Note: Inhaled antibiotic use for chronic suppression of *P. aeruginosa* is acceptable for subjects enrolling in Cohort B.
13. Have, within 30 days prior to Screening, had changes in either the treatment regimen or initiation of treatment with any of the following medications: oral macrolides (eg, azithromycin, erythromycin, or clarithromycin), hypertonic saline, mucolytics, bronchodilator medications, or oral corticosteroids;
14. Have, within the 30 days prior to Screening, received a course of any systemic antibiotics (by any route) for a new active infection at any site, unless assessed as fully resolved and not clinically significant by the Investigator with concurrence of the Medical Monitor;
15. Are, at Screening or during the Screening Period, receiving treatment for active pulmonary infection due to any of the following pathogens: nontuberculous mycobacteria,

Staphylococcus aureus, *Burkholderia cepacia* complex, *Aspergillus* species, or endemic mycoses;

16. Are receiving treatment for allergic bronchopulmonary aspergillosis;
17. Have, within 30 days prior to Screening, received either a systemic corticosteroid at a dose equivalent to >20 mg/day of prednisone (including every other day dosing of >40 mg equivalent) or any immunosuppressive medication or biologic for the treatment of inflammatory or autoimmune disease;
18. Have history of AIDS (human immunodeficiency virus positive with AIDS-defining condition and/or CD4 count <200 cells/mm^3, and/or unstable detectable viral load) or chronic severe liver disease due to hepatitis B virus (HBV) or C virus (HCV) with liver biopsy or radiologic evidence of cirrhosis . If neither of these options are feasible to confirm disease status, ribonucleic acid testing should be performed by the Investigator at Screening;
19. Are, at Screening or during the Screening Period, breastfeeding or planning to become pregnant or breastfeed within the next 2 months;
20. Have, at Screening or during the Screening Period or at the Baseline Visit prior to randomization and first dose of study drug, vital signs considered to be clinically significant by the Investigator, endangering the safe participation of the subject in the study;
21. Have, at Screening or during the Screening Period, abnormal laboratory results. Subjects with values outside of 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.

    Note: Abnormal laboratory results may be repeated once and only once at the discretion of the Investigator.
22. Have, in the opinion of the Investigator, any acute or chronic medical, psychiatric, or behavioral condition or laboratory abnormality such that any of the following apply: the subject is considered not medically stable or in any other way not suitable for the study; participation in the study is not in the subject's best interest, including, but not limited to, concern that participation in the study has the potential to put the subject at undue risk or to interfere with the results of the study or the outcome measures.

STUDY DESIGN AND DURATION:

This is a Phase 2, double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability, and efficacy of AP-PA02 administered by inhalation.

The study will evaluate AP-PA02 administered by inhalation in medically stable NCFB subjects with chronic pulmonary *P. aeruginosa* infection at the time of Screening. A total of 24 eligible subjects who have not received antipseudomonal inhaled antibiotic for a minimum of 3 months prior to Visit 1 will be randomized to Cohort A to receive either AP-PA02 or placebo (2:1 ratio) administered via inhalation. A total of 24 eligible subjects who have received antipseudomonal inhaled antibiotic for a minimum of 3 months prior to Visit 1 will be randomized to Cohort B to

receive either AP-PA02 plus their current antipseudomonal inhaled antibiotic or placebo plus their current antipseudomonal inhaled antibiotic (2:1 ratio) administered via inhalation. Cohort A and Cohort B will be run in parallel. Up to an additional 2 optional cohorts (up to 30 subjects in each cohort) may be included to evaluate different doses and durations of treatment after Data Safety Monitoring Board (DSMB) review. Prior to DSMB review, the maximum study treatment duration will be 10 days for Cohorts A and B and up to 28 days for the optional cohorts.

For Cohort A, eligible subjects will be randomized at the Baseline Visit to receive 1 fractionated dose of AP-PA02 or placebo (1 dose distributed over 2 administrations given 6 hours apart on the same day on Day 1 and 10-12 hours apart each day on the remaining days) for 10 days (Study Days 1 through 10). Subjects will return to the clinic on Days 1, 5, and 10 (Visit 1/Day 1, Visit 2/Day 5, and Visit 3/Day 10) of study drug dosing and approximately 24 hours post last AP-PA02 or placebo dose for safety evaluations and phage recovery sampling, and again 7, 14, and 28 days after the last dose of AP-PA02 or placebo (Visit 4/Day 11, Visit 5/Day 17, Visit 6/Day 24, and Visit 7/Day 38). Subjects will be followed for safety for 4 weeks after the last dose of study drug.

For Cohort B, eligible subjects will be randomized at the Baseline Visit to receive 1 fractionated dose of AP-PA02 or placebo (1 dose distributed over 2 administrations given 6 hours apart on the same day on Day 1 and 10-12 hours apart each day on the remaining days) for 10 days (Study Days 1 through 10) with their current inhaled antipseudomonal antibiotics administered for 28 days (10 days of study drug treatment plus an additional 18 days). Subjects will return to the clinic on Days 1, 5, and 10 (Visit 1/Day 1, Visit 2/Day 5, and Visit 3/Day 10) of study drug dosing and approximately 24 hours post last AP-PA02 or placebo dose for safety evaluations and phage recovery sampling, and again 7, 14, and 28 days after the last dose of AP-PA02 or placebo (Visit 4/Day 11, Visit 5/Day 17, Visit 6/Day 24, and Visit 7/Day 38). Subjects will be followed for safety for 4 weeks after the last dose of study drug.

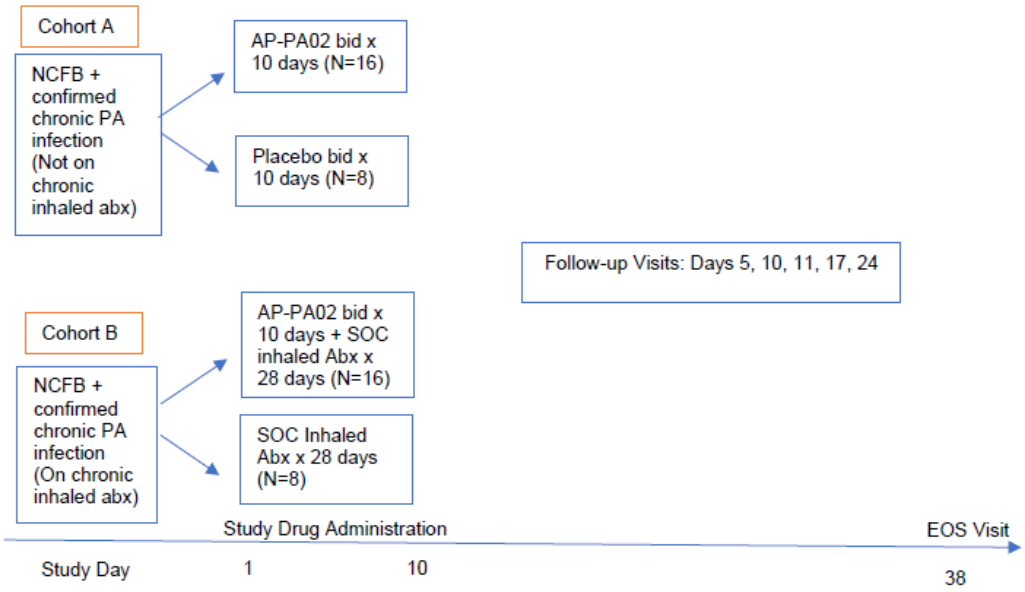
The first 2 subjects in Cohorts A and B will consist of 1 active and 1 placebo subject. Both subjects will be observed for at least 2 days after dosing, and if there are no Grade 2 or greater adverse events (AEs) assessed as treatment-related, dosing for the remaining subjects will proceed.

Safety evaluations after the first dose for each cohort will include vital signs (blood pressure, HR, respiratory rate, and body temperature), SpO_2, 12-lead ECG, and spirometry. The schedule of subsequent assessments during and after treatment is detailed in the Schedule of Assessments.

Visit 7/Day 38 will be the End of Study (EOS) Visit. Safety and an anti-phage antibody titer will be performed at the EOS Visit

Figure S1 displays the enrollment schematic.

Figure S1. Enrollment Schematic: Parallel Design



abx = antibiotic; BID = twice daily; EOS = End of Study; N = number of subjects; NCFB = non-cystic fibrosis bronchiectasis; *P. aeruginosa* = *Pseudomonas aeruginosa*.

Safety Monitoring

If subjects experience any acute AEs post-dose administration (regardless of causal relationship to study drug), the Investigator will determine if they may be observed in the clinic and discharged that day or, in consultation with the Medical Monitor, if they need to be admitted to the hospital for additional observation and/or treatment.

All subjects will be followed for 28 days after the last dose of AP-PA02 or placebo for safety and phage recovery profile, or until resolution or stabilization of AEs or study-related AEs.

AEs Grade 3 or higher assessed by the Investigator as related to study treatment will be reported to the Medical Monitor within 24 hours of awareness. The DSMB will constitute 3 independent physicians with experience in clinical studies and in the management of subjects with chronic pulmonary disease complicated by chronic infections. All DSMB procedures will be documented in a DSMB Charter which will be approved by all members and the Sponsor. The DSMB will conduct unblinded scheduled reviews of all available data after approximately 10% and/or after approximately 50% enrollment. They will also conduct ad hoc reviews as needed. Following each review, they will make recommendations regarding the conduct of the study, including, but not limited to, continuing as planned, modifying procedures, pausing enrollment and/or treatment pending additional information, and discontinuing the study. The planned dose levels and dosing duration after DSMB review may be modified and/or additional cohorts may be added based on emerging information from the current study as well as other ongoing studies. The highest total daily dose will not exceed 4×10^{12} PFU and dosing duration will not exceed 28 days.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

AP-PA02 is a proprietary multi-phage therapeutic candidate. [redacted]

The AP-PA02 dose will be administered to each subject as 2 fractionated doses per treatment day. The dosages shown below are estimated (approximate) plaque-forming units (PFU):

- Each fractionated dose: 1.5×10^{11} PFU;
- Total dose per treatment day: 3×10^{11} PFU; and
- Total dose per 10-day treatment course: 3×10^{12} PFU.

AP-PA02 will be administered in the clinic [redacted] during Visit 1/Day 1 (both doses), Visit 2/Day 5 (morning dose only), and Visit 3/Day 10 (morning dose only). Subjects will administer AP-PA02 at home on all other treatment days.

The placebo is [redacted].

The placebo will be administered in the clinic/at home using the same fractionated dosing schedule and duration as AP-PA02 [redacted]. The placebo will be administered in the clinic during Visit 1/Day 1 (both doses), Visit 2/Day 5 (morning dose only), and Visit 3/Day 10 (morning dose only). Subjects will administer placebo at home on all other treatment days.

On Visit 1/Day 1, clinic staff will administer the first dose of AP-PA02 or placebo. The subject and/or caregiver will administer the second dose of AP-PA02 or placebo with clinic staff observation after the subject has been trained on proper administration. Clinic staff will confirm the subject/caregiver is comfortable with administering AP-PA02 or placebo during this visit. If the subject is not comfortable administering AP-PA02 or placebo, the subject may visit the clinic for study drug administration until he/she or the caregiver is comfortable with proper study drug administration.

Subjects in Cohort A will receive study treatment (AP-PA02 or placebo) administered as 1 dose distributed over 2 administrations given 6 hours apart on the same day on Day 1 and 10-12 hours apart each day on the remaining days for 10 consecutive days, with 28 days of follow-up after the last study drug dose. Subjects in Cohort B will receive study treatment (AP-PA02 or placebo) administered as 1 dose distributed over 2 administrations given 6 hours apart on the same day on Day 1 and 10-12 hours apart each day on the remaining days for 10 consecutive days plus their current antipseudomonal inhaled antibiotic for 28 days (10 days of study drug treatment plus an additional 18 days). Subjects in Cohort B will also have 28 days of follow-up after the last study drug dose.

EFFICACY ENDPOINTS:

The primary efficacy endpoint is sputum *P. aeruginosa* density as measured in sputum samples at 1 week after end of treatment for study drug (Visit 5/Day 17).

The phage recovery endpoint is based on AP-PA02 levels as measured in sputum and venous blood samples at time points specified in the Schedule of Assessments.

The exploratory endpoints include the following:

- Antipseudomonas antibiotic sensitivity of *P. aeruginosa* isolates at specified time points during the study;
- Change in *P. aeruginosa* density from Baseline;
- Change from Baseline of in vitro sensitivity of subject *P. aeruginosa* isolates to AP-PA02 and/or individual phage components;
- Change in spirometry from Baseline;
- Change from Baseline levels of sputum neutrophil elastase; and
- Change in quality of life as assessed by the following questionnaires:
  - Quality of Life-Bronchiectasis Questionnaire;
  - Leicester Cough Questionnaire; and
  - Saint George's Respiratory Questionnaire.

SAFETY VARIABLES:

Safety will be assessed by monitoring AEs, vital signs, SpO_2, laboratory data (chemistry, hematology, urinalysis, and coagulation), anti-phage antibody titer, 12-lead ECGs, spirometry, and physical examination findings.

STATISTICAL ANALYSES:

Analysis Populations

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 1 Baseline and 1 post-Baseline assessment for the primary 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 1 detectable AP-PA02 concentration measurement in sputum, blood, or urine samples.

Efficacy Analyses

The primary efficacy endpoint is the sputum *P. aeruginosa* density as measured in sputum samples at 1 week after end of treatment for study drug (Visit 5/Day 17). The primary efficacy endpoint will be analyzed as logarithmic colony-forming units/g sputum based on the Exploratory Efficacy

Population, and the treatment groups will be compared using a 2-sample t test with 0.05 significance level.

In addition, descriptive statistics will be calculated for the primary efficacy endpoint and all the other efficacy endpoints by treatment group based on the Exploratory Efficacy Population.

All statistical summaries will be descriptive in nature (eg, mean, standard deviation, median, minimum, and maximum for continuous variables and count and percentage for categorical variables). Further details, including the handling of missing data, will be specified in the Statistical Analysis Plan (SAP). The actual values and changes from Baseline will be summarized by visit using descriptive statistics, where appropriate, for all endpoints. Analysis details will be provided in the SAP.

Safety Analyses

Safety will be assessed by the incidence, severity, grade, and relationship of AEs, including clinically significant changes in vital signs, laboratory data, ECGs, and physical examinations. All safety evaluations will be conducted based on the Safety Population.

Descriptive summaries will be provided by treatment group.

SAMPLE SIZE DETERMINATION:

The sample size was determined empirically to meet the objectives of the study. There is no formal power calculation for the sample size. A total of 24 eligible subjects will be randomized to Cohort A to receive either AP-PA02 or placebo (2:1 ratio) administered via inhalation. A total of 24 eligible subjects will be randomized to Cohort B to receive either AP-PA02 plus their current antipseudomonal inhaled antibiotic or placebo plus their current antipseudomonal inhaled antibiotic (2:1 ratio) administered via inhalation. Up to an additional 2 optional cohorts (up to 30 subjects in each cohort) may be included to evaluate different doses and durations of treatment after DSMB review.

SITES: Approximately 30 sites globally

SPONSOR:

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United States
Telephone: +1-310-665-2928 x207

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
CF	Cystic fibrosis
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CT	Computerized tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
FEF_{25-75}	Forced expiratory flow between 25% and 75% of the forced vital capacity
FEV_1	Forced expiratory volume
FVC	Forced vital capacity
GCP	Good Clinical Practice
GLI	Global Lung Initiative
HR	Heart rate
HRCT	High-resolution computerized tomography
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LCQ	Leicester Cough Questionnaire
NCFB	Non-cystic fibrosis bronchiectasis
NIMP	Non-investigational medicinal product
PFU	Plaque-forming units
PRO	Patient-reported outcome
QOL-B	Quality of Life-Bronchiectasis
QTc	Heart rate-corrected QT interval
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SpO_2	Oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper limit of normal

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Introduction

Armata Pharmaceuticals, Inc. (Armata, the Sponsor) is developing a proprietary multi-phage therapeutic candidate (AP-PA02) for the management of non-cystic fibrosis bronchiectasis (NCFB) subjects with chronic respiratory infections associated with *Pseudomonas aeruginosa*.

1.1.1 Non-Cystic Fibrosis Bronchiectasis and Chronic *Pseudomonas aeruginosa* Infection

[redacted]

1.1.2 Phages as Antimicrobials

[redacted]

[redacted]

1.1.2.1 Mechanisms of Action of Phages

[redacted]

1.2 Rationale

[redacted]

[redacted]

1.3 Risk/Benefit

1.3.1 Study Benefits

1.3.1.1 Known Benefits

The clinical benefit of AP-PA02 remains to be established.

1.3.1.2 Potential Benefits

Subjects participating in this study will receive close medical attention and may have benefit regarding the clinical course of their chronic *P. aeruginosa* infection. Results from the proposed study may be useful in developing a new antimicrobial therapy for *Pseudomonas* infections that can be administered at home without the cost or logistical challenges posed by intravenous therapy or the collateral damage to the gut microbiota with systemic therapy.

1.3.2 Study Risks

1.3.2.1 Known Risks

There is limited human experience with AP-PA02. No adverse drug reactions related to study drug have been identified so far.

1.3.2.2 Potential Risks

All therapies have the potential to cause adverse experiences. The risks associated with blood sampling for safety or pharmacokinetic purposes are limited and the volume of blood needed is well below the acceptable limits for adults. Study intervention will be provided in addition to, not in replacement of, standard of care supportive and symptomatic therapy.

The risks of nebulized phage therapy may include bronchial irritation and/or immune response to phages. As such, subjects will be monitored closely on Day 1 of dosing under clinical supervision with regularly scheduled vital sign, spirometry, and AE assessments. In addition, sentinel dosing, individual subject stopping criteria, and study stopping criteria are included as part of the study conduct.

2 STUDY OBJECTIVE

The primary objective is to evaluate the efficacy, safety, and phage kinetics of multiple inhaled doses of AP-PA02 administered as monotherapy and administered in combination with inhaled antibiotics compared to placebo and inhaled antibiotics alone.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 2, double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability, and efficacy of AP-PA02 administered by inhalation.

The study will evaluate AP-PA02 administered by inhalation in medically stable NCFB subjects with chronic pulmonary *P. aeruginosa* infection at the time of Screening. A total of 24 eligible subjects who have not received an antipseudomonal inhaled antibiotic for a minimum of 3 months prior to Visit 1 will be randomized to Cohort A to receive either AP-PA02 or placebo (2:1 ratio) administered via inhalation. A total of 24 eligible subjects who have received an antipseudomonal inhaled antibiotic for a minimum of 3 months prior to Visit 1 will be randomized to Cohort B to receive either AP-PA02 plus their current antipseudomonal inhaled antibiotic or placebo plus their current antipseudomonal inhaled antibiotic (2:1 ratio) administered via inhalation. Cohort A and Cohort B will be run in parallel. Up to an additional 2 optional cohorts (up to 30 subjects in each cohort) may be included to evaluate different doses and durations of treatment after Data Safety Monitoring Board (DSMB) review. Prior to DSMB review, the maximum study treatment duration will be 10 days for Cohorts A and B and up to 28 days for the optional cohorts.

For Cohort A, eligible subjects will be randomized at the Baseline Visit to receive 1 fractionated dose of AP-PA02 or placebo (1 dose distributed over 2 administrations given 6 hours apart on the same day on Day 1 and 10-12 hours apart each day on the remaining days) for 10 days (Study Days 1 through 10). Subjects will return to the clinic on Days 1, 5, and 10 (Visit 1/Day 1, Visit 2/Day 5, and Visit 3/Day 10) of study drug dosing and approximately 24 hours post last AP-PA02 or placebo dose for safety evaluations and phage recovery sampling, and again 7, 14, and 28 days after the last dose of AP-PA02 or placebo (Visit 4/Day 11, Visit 5/Day 17, Visit 6/Day 24, and Visit 7/Day 38). Subjects will be followed for safety for 4 weeks after the last dose of study drug.

For Cohort B, eligible subjects will be randomized at the Baseline Visit to receive 1 fractionated dose of AP-PA02 or placebo (1 dose distributed over 2 administrations given 6 hours apart on the same day on Day 1 and 10-12 hours apart each day on the remaining days) for 10 days (Study Days 1 through 10) with their current inhaled antipseudomonal antibiotic administered for 28 days (10 days of study drug treatment plus an additional 18 days). Subjects will return to the clinic on Days 1, 5, and 10 (Visit 1/Day 1, Visit 2/Day 5, and Visit 3/Day 10) of study drug dosing and approximately 24 hours post last AP-PA02 or placebo dose for safety evaluations and phage recovery sampling, and again 7, 14, and 28 days after the last dose of AP-PA02 or placebo (Visit 4/Day 11, Visit 5/Day 17, Visit 6/Day 24, and Visit 7/Day 38). Subjects will be followed for safety for 4 weeks after the last dose of study drug.

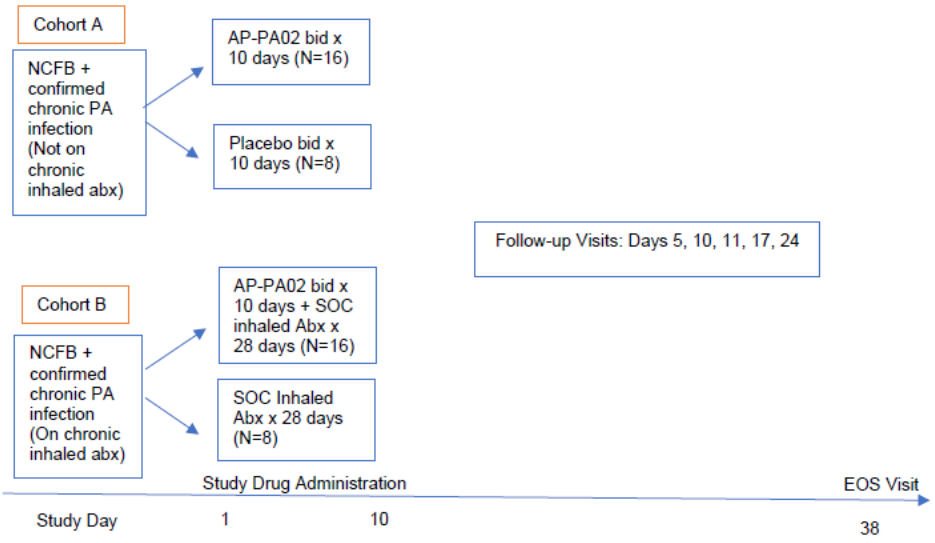
The first 2 subjects in Cohorts A and B will consist of 1 active and 1 placebo subject. Both subjects will be observed for at least 2 days after dosing, and if there are no Grade 2 or greater AEs assessed as treatment-related, dosing for the remaining subjects will proceed.

Safety evaluations after the first dose for each cohort will include vital signs (blood pressure, heart rate [HR], respiratory rate, and body temperature), oxygen saturation (SpO_2), 12-lead electrocardiogram (ECG), and spirometry. The schedule of subsequent assessments during and after treatment is detailed in the Schedule of Assessments (Appendix A).

Visit 7/Day 38 will be the End of Study (EOS) Visit. Safety and an anti-phage antibody titer will be performed at the EOS Visit.

Figure 1 displays the enrollment schematic.

Figure 1. Enrollment Schematic: Parallel Design



abx = antibiotic; BID = twice daily; EOS = End of Study; N = number of subjects; NCFB = non-cystic fibrosis bronchiectasis; *P. aeruginosa* = *Pseudomonas aeruginosa*.

3.1.1 Safety Monitoring

If subjects experience any acute AEs post-dose administration (regardless of causal relationship to study drug), the Investigator will determine if they may be observed in the clinic and discharged that day or, in consultation with the Medical Monitor, if they need to be admitted to the hospital for additional observation and/or treatment.

All subjects will be followed for 28 days after the last dose of AP-PA02 or placebo for safety and phage recovery profile, or until resolution or stabilization of AEs or study-related AEs.

AEs Grade 3 or higher assessed by the Investigator as related to study treatment will be reported to the Medical Monitor within 24 hours of awareness. The DSMB will constitute 3 independent physicians with experience in clinical studies and in the management of subjects with chronic pulmonary disease complicated by chronic infections. All DSMB procedures will be documented in a DSMB Charter which will be approved by all members and the Sponsor. The DSMB will conduct unblinded scheduled reviews of all available data after approximately 10% and/or after approximately 50% enrollment. They will also conduct ad hoc reviews as needed. Following each review, they will make recommendations regarding the conduct of the study, including, but not limited to, continuing as planned, modifying procedures, pausing enrollment and/or treatment pending additional information, and discontinuing the study. The planned dose levels and dosing duration after DSMB review may be modified and/or additional cohorts may be added based on

emerging information from the current study as well as other ongoing studies. The highest total daily dose will not exceed 4×10^{12} PFU and dosing duration will not exceed 28 days.

3.2 Study Indication

The indication for this study is management of NCFB subjects with chronic respiratory infections associated with *P. aeruginosa*.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects who meet all of the following criteria will be considered eligible for enrollment in the study:

1. Are able and willing to comply with the Protocol and provide signed informed consent prior to any study-specific procedures;
2. Are male or female ≥18 years old;
3. Have a body mass index of ≥16.5 kg/m^2;
4. Have findings consistent with bronchiectasis per computerized tomography (CT) (or high-resolution CT [HRCT]);

   Note: A CT or HRCT that demonstrates the above criterion is required during Screening or the Screening Period unless such an examination has been performed within the last 5 years and meets the above criterion.
5. Have microbiological evidence of pulmonary *P. aeruginosa* infection from a sputum sample within the last 24 months. Sputum cultures may be repeated on up to 3 occasions during the Screening Period to document *P. aeruginosa* presence if the initial sputum culture is negative;
6. Are willing and able to provide an induced sputum sample at Screening or during the Screening Period and at designated time points during the study and are willing and able to provide a spontaneously expectorated or induced sputum at all other time points;
7. Have ≥10^4 colony-forming units of *P. aeruginosa* per gram of induced sputum obtained at Screening or during the Screening Period. Up to 3 specimens may be collected to meet this criterion;
8. Have forced expiratory volume (FEV_1) ≥35% of predicted normal for age, gender, race, and height (using Global Lung Function Initiative standards) at Screening (regardless of the timing of the most recent prior administration of short-acting bronchodilator) or during the Screening Period;
9. Have, at the Baseline Visit, stable lung function, as determined by the Investigator, provided that the FEV_1 at the Baseline Visit has not decreased by more than 10% compared to the FEV_1 measured at Screening or during the Screening Period;
10. Have no acute infection or exacerbation of primary disease, as determined by the Investigator, prior to randomization and first dose of study drug;
11. Are able to reproducibly perform spirometry per American Thoracic Society/European Respiratory Society Standards;
12. Have past experience administering inhaled antibiotics and/or feel comfortable administering inhaled antibiotics and/or have a caregiver that is comfortable administering inhaled antibiotics to the subject;
13. For Cohort A, have not received chronic inhaled antipseudomonal antibiotic regimen for at least 3 months prior to Visit 1. For Cohort B, have received chronic inhaled antipseudomonal antibiotic regimen for at least 3 months prior to Visit 1;

14. Are able to comply with study visits and study procedures as judged by the Investigator;
15. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test at the Baseline Visit, with results known prior to randomization and first dose of study drug, if a woman of childbearing potential (as defined in Section 5.6.4);
16. Must agree to use a highly effective method of birth control (defined as those, alone or in combination, that result in a low failure rate [ie, less than 1% per year]) from Screening through 60 days following the last dose of study drug if female or female partner of male subjects, of childbearing potential; and
17. Must agree to use barrier contraception (ie, condoms) from Day 1 through 60 days following the last dose of study drug if male. Male subjects must refrain from donating sperm throughout the study and until 60 days after the last dose of study drug.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible for enrollment in the study:

1. Have previously received 1 or more doses of AP-PA02 in any context, including, but not limited to, prior participation in study AP-PA02-101, prior enrollment in this study, or emergency use (with or without prior authorization);
2. Have a history of lung transplantation;
3. Have a history of primary or acquired immunodeficiency syndromes, including, but not limited to, hypogammaglobulinemia and common variable immunodeficiency;
4. Have a history of cystic fibrosis;
5. Have a history of α1-antitrypsin deficiency;
6. Have a history of pulmonary malignancy (primary or metastatic) or any other malignancy requiring treatment (including, but not limited to, chemotherapy, radiation therapy, or immunotherapy) within 1 year prior to Screening or anticipated during the study period (Exceptions: Basal cell carcinoma of the skin and carcinoma in situ of the cervix surgically excised and assessed as definitely removed);
7. Have, at Screening or during the Screening Period, either of the following findings:
    - A personal history or subject-reported family history of prolonged QT syndrome; or
    - Severe cardiovascular disease such as severe uncontrolled hypertension, unstable ischemic heart disease or cardiac arrhythmia and any other cardiac conditions that would confound the evaluation of safety in the opinion of the Investigator.
8. Have a history of hemoptysis meeting either of the following criteria:
    - Within the 6 months prior to Screening, was hospitalized for management or evaluation of hemoptysis; or
    - Within the 3 months prior to Screening, had hemoptysis totaling greater than 30 mL in a single day.
9. Have, within the 3 months prior to Screening, used supplemental oxygen during the day while at rest;

10. Have, within the 3 months prior to Screening, lost more than 10% of their body weight;
11. Have, within the 2 months prior to Screening, participated in any clinical study involving an investigational drug, an investigational device, or any systemic antibiotic;

    Note: For systemic drugs or antibiotics with a half-life >12 days, the exclusion period is 5 half-lives.
12. Have, within the 30 days prior to Screening, received any intravenous, intramuscular, or oral antipseudomonal antibiotic (Exception: Chronic oral macrolide treatment with a stable dose is permitted);

    Note: Inhaled antibiotic use for chronic suppression of *P. aeruginosa* is acceptable for subjects enrolling in Cohort B.
13. Have, within 30 days prior to Screening, had changes in either the treatment regimen or initiation of treatment with any of the following medications: oral macrolides (eg, azithromycin, erythromycin, or clarithromycin), hypertonic saline, mucolytics, bronchodilator medications, or oral corticosteroids;
14. Have, within the 30 days prior to Screening, received a course of any systemic antibiotics (by any route) for a new active infection at any site, unless assessed as fully resolved and not clinically significant by the Investigator with concurrence of the Medical Monitor;
15. Are, at Screening or during the Screening Period, receiving treatment for active pulmonary infection due to any of the following pathogens: nontuberculous mycobacteria, *Staphylococcus aureus*, *Burkholderia cepacia* complex, *Aspergillus* species, or endemic mycoses;
16. Are receiving treatment for allergic bronchopulmonary aspergillosis;
17. Have, within 30 days prior to Screening, received either a systemic corticosteroid at a dose equivalent to >20 mg/day of prednisone (including every other day dosing of >40 mg equivalent) or any immunosuppressive medication or biologic for the treatment of inflammatory or autoimmune disease;
18. Have history of AIDS (human immunodeficiency virus positive with AIDS-defining condition and/or CD4 count <200 cells/mm^3, and/or unstable detectable viral load) or chronic severe liver disease due to hepatitis B virus (HBV) or C virus (HCV) with liver biopsy or radiologic evidence of cirrhosis. If neither of these options are feasible to confirm disease status, ribonucleic acid testing should be performed by the Investigator at Screening;
19. Are, at Screening or during the Screening Period, breastfeeding or planning to become pregnant or breastfeed within the next 2 months;
20. Have, at Screening or during the Screening Period or at the Baseline Visit prior to randomization and first dose of study drug, vital signs considered to be clinically significant by the Investigator, endangering the safe participation of the subject in the study;
21. Have, at Screening or during the Screening Period, abnormal laboratory results. Subjects with values outside of 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.

Note: Abnormal laboratory results may be repeated once and only once at the discretion of the Investigator.

22. Have, in the opinion of the Investigator, any acute or chronic medical, psychiatric, or behavioral condition or laboratory abnormality such that any of the following apply: the subject is considered not medically stable or in any other way not suitable for the study; participation in the study is not in the subject's best interest, including, but not limited to, concern that participation in the study has the potential to put the subject at undue risk or to interfere with the results of the study or the outcome measures.

4.3 Stopping Criteria

The DSMB will oversee the safety and tolerability of AP-PA02 during the study and determine if it is acceptable to continue. However, safety and tolerability data will be reviewed on an ongoing basis by the Medical Monitor and stopping rules will be applicable starting with dosing of the first subject.

4.3.1 Criteria for Potential Interruption or Discontinuation of Study Drug in Individual Subjects

In the event that any of the following criteria are encountered, the Investigator will review the AE with the Medical Monitor as soon as feasible. The Investigator will hold the next administration pending that review. The Investigator and Medical Monitor in consultation with the Sponsor will decide whether to continue to hold study treatment pending additional information or to discontinue study treatment.

- ≥Grade 3 AE or laboratory abnormality per Common Terminology Criteria for AEs (CTCAE) version 5.0 considered attributable to AP-PA02 (confirmed by unblinding). If the event or laboratory test is not listed in the CTCAE, the event or laboratory test should be graded by applying the CTCAE guidelines detailed in Section 8.1.3;

  Note: Clinically significant laboratory abnormalities classified per above should be confirmed with a repeat test within 24 hours.

- Any serious AE (SAE) considered attributable to AP-PA02 (confirmed by unblinding); or
- Acute bronchospasm, defined as a decrease in absolute FEV_1 of ≥15% accompanied by symptoms requiring medical intervention, occurring from the Baseline value up to 4 hours following study drug administration and persisting following administration of a short-acting bronchodilator.

Any subject who prematurely discontinues from study drug, will have documented the reason and date of discontinuation in the electronic case report form (eCRF) and the subject should be encouraged to continue to complete all safety and key efficacy assessments at subsequent study visits. For subjects who do not agree to participate in subsequent study visits, study staff should make every effort to complete the full panel of assessments scheduled for the Early Termination (ET) Visit.

4.3.2 Criteria for Ad Hoc Data Safety Monitoring Board Review of Study

In the event that any of the following criteria are encountered, the DSMB may, as described in the DSMB Charter, convene to review available data and make recommendations, including but not limited to, if the cohort should stop or if it is necessary to pause the study, enrollment, or treatment and/or make recommendations to modify the Protocol (ie, decrease or change the dose of study drug, modify safety monitoring):

- If any unacceptable toxicity (as determined by the Investigator or Sponsor's Medical Monitor) occurs;
- If ≥1 SAE considered attributable to AP-PA02 (confirmed by unblinding) occurs; or
- If ≥2 of all treated subjects experience similar SAEs or Grade 3 (CTCAE version 5.0) considered attributable to AP-PA02 (confirmed by unblinding).

  Note: All ≥Grade 3 (CTCAE version 5.0) laboratory abnormalities should be confirmed with a repeat test within 24 hours.

If the DSMB recommends, and the Sponsor then implements, stopping study treatment and, subsequently, the Sponsor, independent of or following a DSMB recommendation, proposes to restart the study, a substantial amendment will be submitted to regulatory agencies and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs). The study will not restart until the amendment has been approved by regulatory agencies and IRBs/IECs. These requirements are not applicable if the Sponsor pre-emptively pauses study treatment for subject safety pending DSMB review and the DSMB recommends resuming study treatments and/or any study modifications recommended do not represent substantial Protocol changes.

4.4 Withdrawal or Modification of Individual Subject Study Participation

Participation of a subject in this clinical study will be discontinued for any of the following reasons:

- The subject or legally authorized representative withdraws consent or requests discontinuation from the study for any reason;
- The subject becomes pregnant; or
- The subject has not demonstrated to clinic staff that he/she can properly administer study drug, the subject has no appropriate caregiver who has demonstrated that he/she can properly administer study drug to the subject, or the subject is not able or willing to return to the clinic for study drug administration to ensure that the subject properly receives study drug as per the Protocol.

The Investigator may, with concurrence of the Medical Monitor or Sponsor, discontinue or modify a subject's study participation for any of the following reasons:

- Occurrence of any AE (whether or not attributed to study treatment), medical condition, or circumstance that does not allow the subject to adhere to the requirements of the Protocol or continued participation is not in the best interest of the subject; or
- Subject failure to comply with Protocol requirements or study-related procedures.

Subjects will be considered lost to follow-up if, after completing study treatment, they fail to attend a required visit or are unresponsive despite 3 attempts to reach them by telephone, text message,

email, and/or regular postal mail. Such subjects may, with the concurrence of the Sponsor, be terminated from study participation and notification sent by registered mail to the last known address. These contact attempts will be documented in both the study record and the subject's medical record.

Subjects who discontinue prematurely from the study or whose participation is modified will be strongly encouraged to complete the full panel of safety assessments scheduled for the ET Visit. The reason for subject withdrawal must be documented in the eCRF.

Withdrawn or lost to follow-up subjects may be replaced to ensure adequate numbers of evaluable subjects at the discretion of the Sponsor. Subjects who discontinue for study drug-related safety or tolerability reasons will not be replaced.

4.4.1 Termination of the Study

The Sponsor may terminate the study at any time and for any reason, including, but not limited to, recommendation by the DSMB, new nonclinical information regarding the study treatment, or if required by regulatory authorities.

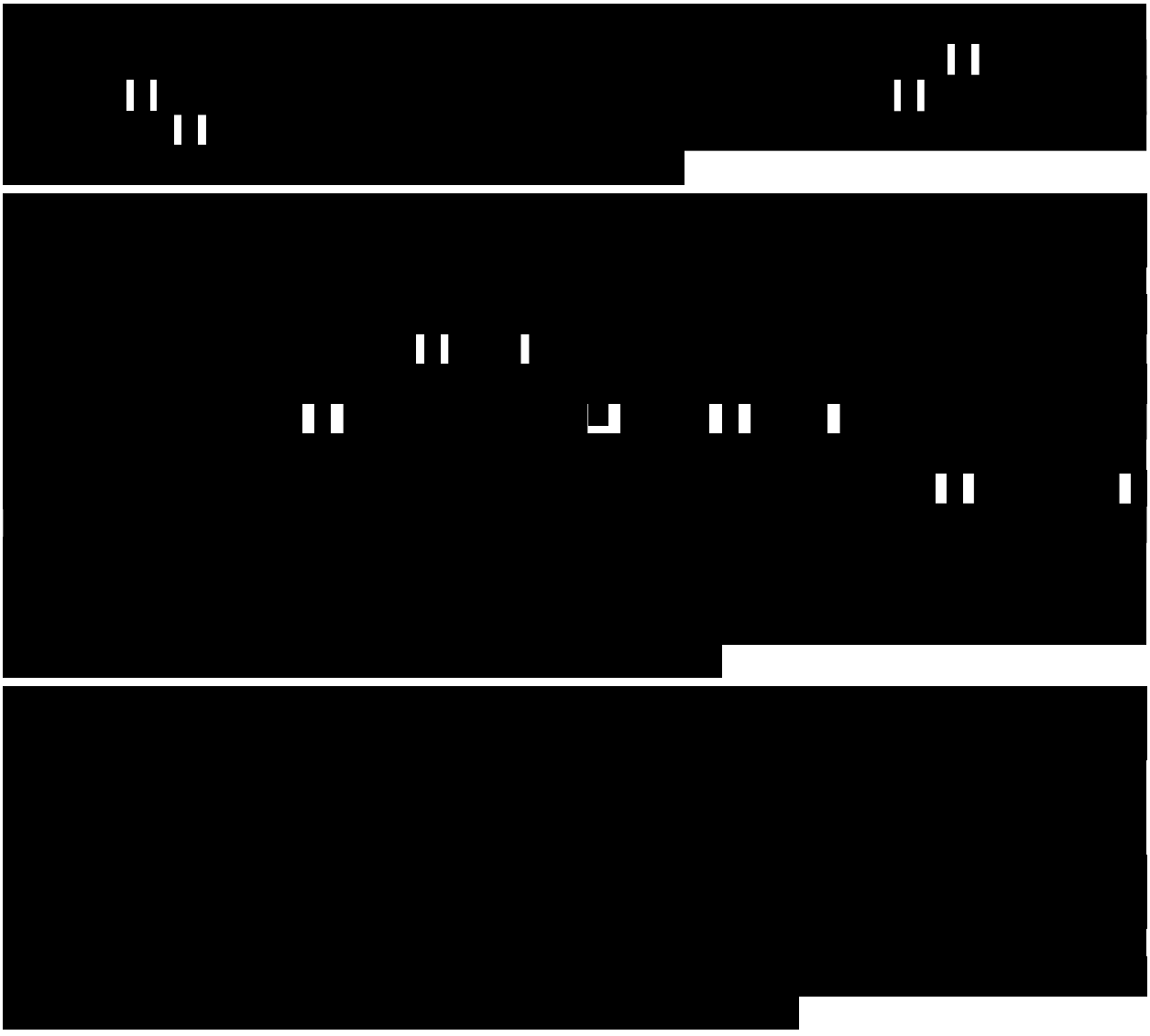
Depending on the circumstances, termination procedures may or may not include completion of study treatment as assigned for all subjects who have received at least 1 dose. After a subject receives their last treatment, all EOS treatment safety evaluations will be completed.

5 STUDY TREATMENTS

5.1 Treatment Groups

Cohort A subjects will receive AP-PA02 or placebo. Cohort B subjects will receive AP-PA02 plus their current antipseudomonal inhaled antibiotic or placebo plus their current antipseudomonal inhaled antibiotic. See Figure 1 for the enrollment schematic.

5.2 Rationale for Dosing



5.3 Randomization and Blinding

A total of 24 eligible subjects will be randomized to Cohort A to receive either AP-PA02 or placebo (2:1 ratio) administered via inhalation. A total of 24 eligible subjects will be randomized to Cohort B to receive either AP-PA02 plus their current antipseudomonal inhaled antibiotic or placebo plus their current antipseudomonal inhaled antibiotic (2:1 ratio) administered via

inhalation. Up to an additional 2 optional cohorts (up to 30 subjects in each cohort) may be included to evaluate different doses and durations of treatment after DSMB review.

This is a double-blind study. All subjects, Investigators, and study and Sponsor personnel involved in the conduct of the study will be blinded to subject treatment assignment. There will be a designated unblinded statistician who will generate and have access to the randomization code. The unblinded statistician and other personnel who may become unblinded will not otherwise participate in any study procedures.

5.4 Breaking the Blind

Unblinding at the request of the Investigator should occur only in the event of a severe AE or SAE that is reasonably assessed as treatment related and for which it is necessary to know the treatment assignment to determine an appropriate course of therapy for the subject. If the Investigator must identify the treatment assignment of an individual subject, the Investigator or qualified designee should request the treatment assignment from the centralized randomization system. They should not attempt to get this information from the site's unblinded study team. The Investigator is advised to not reveal the treatment assignment to any other site, Sponsor, or Contract Research Organization personnel.

Whenever possible, prior to proceeding with unblinding, the Investigator will contact the Sponsor to discuss the need to break the blind. The Investigator will notify the Sponsor as soon as is practical in the event of the study blind being broken and will document the reason. In the event this is not possible, the Investigator should contact the Sponsor as soon as possible to discuss the event without revealing the treatment assignment. The Investigator must document the subject identification, the date and time of breaking the blind, and must clearly explain the reasons for breaking the blind.

Medically necessary care should not be delayed for unblinding information (ie, the Investigator should treat the subject based on the subject's signs/symptoms without waiting for the unblinding process to be completed).

Subjects who are unblinded and discontinue study drug should continue to complete all safety assessments at subsequent study visits.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

5.5.2 Study Drug Preparation and Dispensing

[redacted]

Study drug will be administered in the clinic by qualified site personnel/at home by the subject via the designated study nebulizer, until all study drug solution has been administered. [redacted] The subject and/or subject's caregiver will be trained on administration of study drug for administration at home. The subject will receive study drug doses for home administration on Visit 1/Day 1 for treatment Days 2 through 4 and on Visit 2/Day 5 for treatment Days 5 (second dose) through 9, and on Visit 3/Day 10 for treatment Day 10 (second dose).

[redacted]

5.5.3 Study Drug Administration

The AP-PA02 dose will be administered to each subject as 2 fractionated doses per treatment day. The dosages shown below are estimated (approximate) PFU:

- Each fractionated dose: 1.5×10^{11} PFU;
- Total dose per treatment day: 3×10^{11} PFU; and
- Total dose per 10-day treatment course: 3×10^{12} PFU.

AP-PA02 will be administered in the clinic [redacted] during Visit 1/Day 1 (both doses), Visit 2/Day 5 (morning dose only), and Visit 3/Day 10 (morning dose only). Subjects will administer AP-PA02 at home on all other treatment days.

The placebo will be administered in the clinic/at home using the same fractionated dosing schedule and duration as AP-PA02 and [redacted]. The placebo will be administered in the clinic during Visit 1/Day 1 (both doses), Visit 2/Day 5 (morning dose only), and Visit 3/Day 10 (morning dose only). Subjects will administer placebo at home on all other treatment days.

On Visit 1/Day 1, clinic staff will administer the first dose of AP-PA02 or placebo. The subject and/or caregiver will administer the second dose of AP-PA02 or placebo with clinic staff observation after the subject has been trained on proper administration. Clinic staff will confirm

the subject/caregiver is comfortable with administering AP-PA02 or placebo during this visit. If the subject is not comfortable administering AP-PA02 or placebo, the subject may visit the clinic for study drug administration until he/she or the caregiver is comfortable with proper study drug administration.

Subjects in Cohort A will receive study treatment (AP-PA02 or placebo) administered as 1 dose distributed over 2 administrations given 6 hours apart on the same day on Day 1 and 10-12 hours apart each day on the remaining days on 10 consecutive days, with 28 days of follow-up after the last study drug dose. Subjects in Cohort B will receive study treatment (AP-PA02 or placebo) administered as 1 dose distributed over 2 administrations given 6 hours apart on the same day on Day 1 and 10-12 hours apart each day on the remaining days for 10 consecutive days plus their current antipseudomonal inhaled antibiotic for 28 days (10 days of study drug treatment plus an additional 18 days). Subjects in Cohort B will also have 28 days of follow-up after the last study drug dose.

5.5.4 Treatment Compliance

Details of the date and time when the study drug is administered, along with any deviation from the procedure described in this Protocol, will be recorded in the subject's source documents and the eCRF for the days study drug is administered in the clinic. For the days subjects administer study drug at home, treatment compliance will be documented in a subject diary and will be assessed by the diary entries, including date, times, and whether the complete dose was administered, and returned study drug.

5.5.5 Storage and Accountability

[redacted].

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 the Sponsor. The study drug must be dispensed only at the institution(s) specified on form Food and Drug Administration (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.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Systemic corticosteroids at a dose equivalent to >20 mg/day of prednisone (including every other day dosing of >40 mg equivalent) or any immunosuppressive medication or biologic for the treatment of inflammatory or autoimmune disease is prohibited.

5.6.2 Restricted Medications and/or Procedures

Subjects may continue on an oral macrolide treatment (eg, azithromycin, erythromycin, or clarithromycin), hyper tonic saline, mucolytics, bronchodilator medications, or oral corticosteroids with a stable dose as long as it was not initiated within the 30 days prior to Screening.

5.6.3 Documentation of Prior and Concomitant Medication Use

Medications used within 30 days prior to Screening will be recorded. The coronavirus disease 2019 vaccination status (including type of vaccine and administration date[s]) of all subjects will be recorded as a prior (if received prior to dosing) and/or concomitant medication in the eCRF.

Any treatment given in addition to the study drug during the study will be regarded as a concomitant medication and must be recorded on the appropriate eCRF.

Any relevant medications received in the 28 days prior to randomization must be recorded on the appropriate eCRF, along with the reason for use, dates of administration, and dosages.

Concomitant medications, including over-the-counter medications and herbal supplements, should be kept to a minimum during the study. However, if these are considered necessary for the subject's welfare and are unlikely to interfere with the study drug, they may be given at the discretion of the Investigator and recorded in the subject's source documents and the eCRF.

5.6.4 Contraception

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;
- Intrauterine hormone-releasing system;
- Bilateral tubal occlusion;
- Vasectomized partner (provided that partner is the sole sexual partner and has received medical assessment of the surgical success); and
- Sexual abstinence. Sexual abstinence must be true abstinence which is the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptom-thermal, post-ovulation methods), declaration of abstinence for the duration of the study, 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 study. 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 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. Male subjects must refrain from donating sperm throughout the study and until 60 days after the last dose of study drug.

6 STUDY PROCEDURES

Study procedures will follow the Schedule of Assessments and Timing of Sample Collection and Procedures for the Treatment Period (Appendix A).

7 EFFICACY ASSESSMENTS

7.1 Efficacy Endpoints

The primary efficacy endpoint is sputum *P. aeruginosa* density as measured in sputum samples at 1 week after end of treatment for study drug (Visit 5/Day 17).

The phage recovery endpoint is based on AP-PA02 levels as measured in sputum and venous blood samples at time points specified in the Schedule of Assessments (Appendix A).

The exploratory endpoints include the following:

- Antipseudomonas antibiotic sensitivity of *P. aeruginosa* isolates at specified time points during the study;
- Change in *P. aeruginosa* density from Baseline;
- Change from Baseline of in vitro sensitivity of subject *P. aeruginosa* isolates to AP-PA02 and/or individual phage components;
- Change in spirometry from Baseline;
- Change from Baseline levels of sputum neutrophil elastase; and
- Change in quality of life as assessed by the following questionnaires:
  - Quality of Life-Bronchiectasis (QOL-B) Questionnaire;
  - Leicester Cough Questionnaire (LCQ); and
  - Saint George's Respiratory Questionnaire.

7.2 Sputum Culture

Sputum for microbiology will be processed at a central laboratory for all visits. Quantitative cultures and sensitivity will be performed. *P. 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 spontaneous expectoration or induction will be performed per standardized methodology at the time points specified in the Schedule of Assessments and Timing of Sample Collection and Procedures for the Treatment Period (Appendix A). Induced sputum samples for culture will be required at Screening, Baseline, Visit 2/Day 5, Visit 3/Day 10, Visit 4/ Day 11, Visit 5/Day 17, Visit 6/Day 24, and Visit 7/EOS/Day 38. Standardized sputum induction methodology will 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 containers and insulated transport containers in which to carry their specimens to the clinic.

7.2.1 Antipseudomonal Antibiotic Sensitivity

Antipseudomonal antibiotic sensitivity will be tested by the central microbiology laboratory at the visits indicated in the Schedule of Assessments (Appendix A).

7.2.2 Sensitivity of *Pseudomonas aeruginosa* Isolates to AP-PA02

The change in *P. aeruginosa* isolate sensitivity to AP-PA02 between initiation of study drug and the last isolation of *P. aeruginosa* from sputum will be assessed as indicated in the Schedule of Assessments (Appendix A).

7.3 Sputum Phage Titer

Sputum for phage titer will be obtained as designated in the Schedule of Assessments and Timing of Sample Collection and Procedures for the Treatment Period (Appendix A). Induced sputum samples will be required on Visit 1/Day 1, Visit 2/Day 5, Visit 3/Day 10, Visit 4/Day 11, Visit 5/Day 17, Visit 6/Day 24, and Visit 7/EOS/Day 38. Sputum samples will be obtained in the morning on Visit 4/Day 11.

7.4 Blood Phage Titer

Blood for phage titer will be obtained as designated in the Schedule of Assessments and Timing of Sample Collection and Procedures for the Treatment Period (Appendix A). When blood samples are scheduled at time points when safety laboratories and phage titer samples are also to be collected, safety laboratory samples are to be collected first, followed by phage titer samples. Blood samples will be obtained in the morning on Visit 4/Day 11.

7.5 Urine Phage Titer

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

7.6 Change in Spirometry

Spirometry will be performed per American Thoracic Society/European Respiratory Society Standards[28,29,30,31,32] and evaluated locally at the clinical study site. FEV_1, forced vital capacity (FVC), and forced expiratory flow between 25% and 75% of the FVC (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.

7.7 Daily Symptom Diary

A standardized subject diary will be provided to each study subject to collect subject symptoms following the administration of study drug. Solicited symptoms assessed may include but are not limited to: difficulty breathing, cough, sputum production, color of sputum, hemoptysis, feeling feverish, and/or fatigue. The 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 for review and the diary will be collected at the End of Study Visit.

7.8 Biomarkers

Biomarkers, including sputum neutrophil elastase, will be tested by the central laboratory as indicated in the Schedule of Assessments and Timing of Sample Collection and Procedures for the Treatment Period (Appendix A).

7.9 Questionnaires

Subjects will complete questionnaires according to the Schedule of Assessments (Appendix A).

7.9.1 Quality of Life-Bronchiectasis Questionnaire

The QOL-B Questionnaire is a self-administered PRO measure designed specifically for subjects with bronchiectasis.[33] This PRO contains 37 items on 8 scales to assess respiratory symptoms, functioning, and health-related quality of life of subjects within the past week.

7.9.2 Leicester Cough Questionnaire

The LCQ is a 19 item self-completed quality of life measure of chronic cough which is responsive to change.[34] Subjects will respond to each item using a 7-point Likert response scale.

7.9.3 Saint George's Respiratory Questionnaire

The Saint George's Respiratory Questionnaire is a measure to assess impaired health and perceived well-being (quality of life).[35] The Saint George's Respiratory Questionnaire was designed to allow for comparative measurements of health and quantify changes in health following treatment. Scores of 3 components (symptoms, activity, and impacts [on daily life]) and total score will be evaluated.[36]

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory test variables, will be monitored and documented from the time of first dose of AP-PA02 or placebo until the EOS Visit. Subjects should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study treatment. Beginning at the date of the first dose of study drug, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present prior to the first dose of the study drug should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at Baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present prior to the first dose of study drug and significantly worsen during the study should be reported as AEs, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality;
- If action taken with the study drug is required as a result of the abnormality; or
- Based on the clinical judgment of the Investigator.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal

relationship between a medicinal product and an AE is at least a reasonable possibility, ie the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For AP-PA02, the reference safety information is included in the Investigator's Brochure currently in force. The reference safety information will be reviewed yearly, and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.1.3 Assessment of Adverse Events by the Investigator

The severity of all AEs should be graded according to the CTCAE version 5.0. For those AE terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
- CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated; or
- CTCAE Grade 5: Death related to the AE.

Causality assessment

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant drug-

  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and pharmacokinetics of the study drug-

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from Baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency/drug abuse.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to the Sponsor/designee within 24 hours of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the Investigator considers related to study drug must be reported to the Sponsor/designee. Instructions for the reporting of SAEs are outlined in the study reference instructions provided to the Investigator.

Follow-up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form and submit any supporting documentation (eg, subject discharge summary or autopsy reports).

8.4 Pregnancy Reporting

If a subject becomes pregnant during the study or within the safety follow-up period defined in the Protocol, the Investigator is to stop dosing with study drug(s) immediately and the subject should be withdrawn from the study. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to the Sponsor/designee within 24 hours of knowledge of the event.

If the female partner of a male subject becomes pregnant while the subject is receiving study drug or within the safety follow-up period defined in the Protocol, the Investigator should notify the Sponsor/designee as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the Investigator will report the information to the Sponsor/designee. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the FDA, applicable competent authorities in all the Member States concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA, applicable competent authorities concerned, and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational medicinal products.

Expedited reporting of SUSARs related to comparators is also required in line with the requirements above. Expedited reporting of SUSARs related to non-investigational medicinal products (NIMPs) (and any other NIMPs) is not required. Listings of cases related to NIMPs will be included in the Development Safety Update Report.

8.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the Protocol. Clinical judgement should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the subject has taken additional dose(s), or the Investigator has reason to suspect that the subject has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the Protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, subject, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors. Cases of subjects missing doses of investigational product are not considered reportable as medication errors.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situation report form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported to the Sponsor/designee within 24 hours of knowledge of the event. All AEs associated with these special situation reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

8.7 Anti-Phage Antibody Titer

The anti-phage antibody titer will be assessed as indicated in the Schedule of Assessments (Appendix A).

8.8 Spirometry

Spirometry will be performed per American Thoracic Society/European Respiratory Society Standards[28,29,30,31,32] 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. Study eligibility will be based on percent predicted value using Global Lung Initiative (GLI) standards, which requires race and ethnicity information as part of the GLI calculation. Spirometry will be assessed according to the Schedule of Assessments and Timing of Sample Collection and Procedures for the Treatment Period (Appendix A). Spirometry will be collected prior to sputum induction on non-Treatment Period Visits.

8.9 Oxygen Saturation

SpO_2 will be assessed according to the Schedule of Assessments and Timing of Sample Collection and Procedures for the Treatment Period (Appendix A).

8.10 Clinical Laboratory Evaluations

Clinical laboratory evaluations include chemistry, hematology, urinalysis, and coagulation and will be assessed according to the Schedule of Assessments and Timing of Sample Collection and Procedures for the Treatment Period (Appendix A). See Appendix B for a list of clinical laboratory analytes.

Abnormal laboratory results may be repeated once and only once at the discretion of the Investigator. 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.

8.11 Vital Signs

Vital signs include blood pressure, HR, respiratory rate, and body temperature and will be assessed according to the Schedule of Assessments and Timing of Sample Collection and Procedures for the Treatment Period (Appendix A).

8.12 Twelve-Lead Electrocardiograms

Twelve-lead ECGs will be performed according to the Schedule of Assessments and Timing of Sample Collection and Procedures for the Treatment Period (Appendix A). The Fridericia formula for calculating QTc will be used.

8.13 Physical Examinations

A full physical examination will be performed at the Screening Visit, Baseline Visit, and the EOS Visit. A symptom-directed physical examination will be performed at the other visits according to the Schedule of Assessments (Appendix A).

8.14 Height and Weight

Height and weight will be collected according to the Schedule of Assessments (Appendix A). Height will be collected at the Screening Visit only and will be used to calculate body mass index and percent predicted spirometry values by GLI standards.

8.15 Pregnancy Testing

For women of childbearing potential only, a serum pregnancy test will be performed during the Screening Period and a urine pregnancy test will be performed at the other visits as indicated in the Schedule of Assessments (Appendix A).

9 STATISTICS

9.1 Analysis Populations

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 1 Baseline and 1 post-Baseline assessment for the primary 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 1 detectable AP-PA02 concentration measurement in sputum, blood, or urine samples.

9.2 Statistical Methods

9.2.1 Analysis of Efficacy

9.2.1.1 Efficacy Analyses

The primary efficacy endpoint is the sputum *P. aeruginosa* density as measured in sputum samples at 1 week after end of treatment for study drug (Visit 5/Day 17). The primary efficacy endpoint will be analyzed as logarithmic colony-forming units/g sputum based on the Exploratory Efficacy Population, and the treatment groups will be compared using a 2-sample t test with 0.05 significance level.

In addition, descriptive statistics will be calculated for the primary efficacy endpoint and all the other efficacy endpoints by treatment group based on the Exploratory Efficacy Population.

All statistical summaries will be descriptive in nature (eg, mean, standard deviation, median, minimum, and maximum for continuous variables and count and percentage for categorical variables). Further details, including the handling of missing data, will be specified in the Statistical Analysis Plan (SAP). The actual values and changes from Baseline will be summarized by visit using descriptive statistics, where appropriate, for all endpoints. Analysis details will be provided in the SAP.

9.2.2 Analysis of Safety

Safety will be assessed by the incidence, severity, grade, and relationship of AEs, including clinically significant changes in vital signs, laboratory data, ECGs, and physical examinations. All safety evaluations will be conducted based on the Safety Population.

Descriptive summaries will be provided by treatment group.

9.2.3 Interim Analysis

No formal interim analysis is planned for the study.

9.2.4 Sample Size Determination

The sample size was determined empirically to meet the objectives of the study. There is no formal power calculation for the sample size. A total of 24 eligible subjects will be randomized to Cohort A to receive either AP-PA02 or placebo (2:1 ratio) administered via inhalation. A total of 24 eligible subjects will be randomized to Cohort B to receive either AP-PA02 plus their current antipseudomonal inhaled antibiotic or placebo plus their current antipseudomonal inhaled antibiotic (2:1 ratio) administered via inhalation. Up to an additional 2 optional cohorts (up to 30 subjects in each cohort) may be included to evaluate different doses and durations of treatment after DSMB review.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (CFR) (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and AEs; and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The EOS ("study completion") is defined as the date of the last Protocol-specified visit/assessment (including telephone contact) for the last subject in the study. Subjects alive at the EOS who require further follow-up may be entered into a separate long-term follow-up study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board/Independent Ethics Committee

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The Protocol, Investigator's Brochure, informed consent form (ICF), advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB/IEC prior to participation of subjects in research studies. Prior to study onset, the Protocol, any Protocol Amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB/IEC.

No drug will be released to the site for dosing until written IRB/IEC authorization has been received by the Sponsor.

It is the responsibility of the Sponsor or their designee to obtain the approval of the responsible ethics committees according to the national regulations.

The study will only start in the respective sites once the respective committee's written approval has been given.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, auditors, the IRB, and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

11.4 Subject Card

On enrollment in the study, the subject will receive a subject card to be carried at all times. The subject card will state that the subject is participating in a clinical research study, type of treatment, number of treatment packs received, and contact details in case of an SAE.

11.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the Protocol, ICH GCP, Directive 2001/20/EC, applicable regulatory requirements, and the Declaration of Helsinki and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well-organized, and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: Protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and Protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the CRA and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain

written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out subject liability insurance for all subjects who have given their consent to the clinical study. This coverage is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

11.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a Clinical Trial Authorisation (CTA).

The study will commence (ie, initiation of study centers) when the CTA and favorable Ethics opinion have been received.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study Protocol will be communicated to the Investigators by the Sponsor or designee. All Protocol Amendments will undergo the same review and approval process as the original Protocol. A Protocol Amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

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APPENDIX A: SCHEDULE OF ASSESSMENTS AND TIMING OF SAMPLE COLLECTION AND PROCEDURES FOR THE TREATMENT PERIOD

Table 1. Schedule of Assessments

	Screening Period	Baseline	Treatment Period			Safety Follow-Up Period				Early Termination
Visit	**Screening**	**Baseline**	**1**	**2**	**3**	**4**	**5**	**6**	**7/EOS**	**ET**
Day	**-35 to -2**	**-7 to -1**	**1**	**5**	**10**	**11**	**17**	**24**	**38**	**U**
Visit Window							**(±3d)**	**(±3d)**	**(±3d)**	
Informed consent[a]	X									
Inclusion/exclusion criteria	X	X	X[b]							
Demographic information	X									
Medical/surgical history	X									
Prior/concomitant medications	X		X	X	X	X	X	X	X	X
HIV antibody, HBsAg, and HCV by RNA[c]	X									
Weight and height[c]	X									
Physical examination[d]	X	X	X	X	X	X	X	X	X	X
Vital signs and SpO_2[e]	X	X	X	X	X	X	X	X	X	X
Spirometry[f]	X	X	X	X	X	X	X	X	X	X
CT or HRCT[g]	X									
Pregnancy test[h]	X	X							X	
12-lead ECG	X		X						X	X
Clinical laboratory assessments[i]	X	X	X	X	X		X	X		X
Urinalysis	X	X		X	X					X
Induced sputum sample (required)	*	*	*	*	*	*	*	*	*	*
Sputum culture[k]	X[j]	X		X	X	X	X	X	X	X
Sputum phage titer[l]		X	X	X	X	X	X	X	X	X
Antipseudomonal antibiotic sensitivity	X	X						X	X	X

Sensitivity *of P. aeruginosa* isolates to AP-PA02	X							X	X	X
Biomarkers		X	X	X	X	X	X	X	X	X
Expectorated sputum sample (if able to provide)		*	*	*	*	*	*	*	*	*
Sputum culture[k]		X		X	X	X	X	X	X	X
Sputum phage titer		X	X	X	X	X	X	X	X	X
Blood phage titer[m]		X	X	X	X	X	X	X	X	X
Urine phage titer[n]		X				X				X
Randomization		X								
Distribute sputum and urine collection containers			X							
Daily symptom diary		Dispense	Review	Review	Review	Review	Review	Review	Collect	**Collect**

Table 1. Schedule of Assessments (Continued)

	Screening Period	Baseline	Treatment Period			Safety Follow-Up Period				Early Termination
Visit	**Screening**	**Baseline**	**1**	**2**	**3**	**4**	**5**	**6**	**7/EOS**	**ET**
Day	**-35 to -2**	**-7 to -1**	**1**	**5**	**10**	**11**	**17**	**24**	**38**	**U**
Visit Window							**(±3d)**	**(±3d)**	**(±3d)**	
Dispense study drug for home administration[o]			X	X	X					
Study drug administration training			X							
Study drug administration[p]			X	X	X					
Antibiotic administration[q]		X	X	X	X	X	X	X		
QOL-B Questionnaire		X				X		X		
LCQ		X				X		X		
Saint George's Respiratory Questionnaire		X							X	
Anti-phage antibody titer		X						X	X	X
AEs/SAEs[r]	X	X	X	X	X	X	X	X	X	X

Note: If a subject withdraws prematurely from the study, study staff should make every effort to complete the full panel of assessments scheduled for the ET Visit. See the Timing of Sample Collection and Procedures for the Treatment Period table for sample collection and procedure timing during the Treatment Period. The Treatment Period may be up to 28 days for the optional cohorts.

a. Signed informed consent must be obtained before any study-related procedures are performed.
b. Any updates since the Baseline Visit will be assessed.

c. HIV antibody, HBsAg, and HCV antibody testing will be performed at Screening, only if status is unknown. Height will be collected at the Screening Visit only and will be used to calculate body mass index and percent predicted spirometry values by GLI standards.
d. A full physical examination will be performed at the Screening Visit, Baseline Visit, and the EOS Visit. A symptom-directed physical examination will be performed at the other visits.
e. Vital signs include blood pressure, heart rate, respiratory rate, and body temperature.
f. FEV_1, FVC, and FEF_{25-75} will be collected. Actual liter values will be recorded. Study eligibility will be based on percent predicted value using GLI standards, which requires race and ethnicity information as part of the GLI calculation. Spirometry will be collected prior to sputum induction on non-Treatment Period Visits.
g. A CT or HRCT that demonstrates bronchiectasis per Inclusion Criterion 4 is required during the Screening Period unless such an examination has been performed within the last 5 years and meets the criteria in Inclusion Criterion 4.
h. For women of childbearing potential only, a serum pregnancy test will be performed during the Screening Period and a urine pregnancy test will be performed at the other visits.
i. Includes clinical chemistry, hematology, and coagulation. See Appendix B for a list of clinical laboratory analytes. Abnormal laboratory results during the Screening Period may be repeated once and only once at the discretion of the Investigator. 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.
j. Subjects must have microbiological evidence of pulmonary *P. aeruginosa* infection from a sputum sample within the last 24 months. Must have $\geq 10^4$ CFU of *P. aeruginosa* per gram of induced sputum obtained at Screening or during the Screening Period. Sputum cultures may be repeated on up to 3 occasions during the Screening Period to document *P. aeruginosa* presence if the initial sputum culture is negative.
k. Induced sputum samples for culture will be required at Screening, Baseline, Visit 2/Day 5, Visit 3/Day 10, Visit 4/Day 11, Visit 5/Day 17, Visit 6/Day 24, and Visit 7/EOS/Day 38. 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.
l. Induced sputum samples will be required on Visit 1/Day 1, Visit 2/Day 5, Visit 3/Day 10, Visit 4/Day 11, Visit 5/Day 17, Visit 6/Day 24, and Visit 7/EOS/Day 38. Sputum samples will be obtained in the morning on Visit 4/Day 11.
m. When blood samples are scheduled at time points when safety laboratories and phage titer samples are also to be collected, safety laboratory samples are to be collected first, followed by phage titer samples. Blood samples will be obtained in the morning on Visit 4/Day 11.
n. Date and time will be recorded for each urine sample collection at the designated time points.
o. The subject will receive study drug doses for home administration on Visit 1/Day 1 for treatment Days 2 through 4 and on Visit 2/Day 5 for treatment Days 5 (second dose) through 9 and on Visit 3/Day 10 for treatment Day 10 (second dose).
p. The first 2 subjects in Cohorts A and B will consist of 1 active and 1 placebo subject. Both subjects will be observed for at least 2 days after dosing and if there are no Grade 2 or greater AEs assessed as treatment-related, dosing for the remaining subjects will proceed. Study drug will be administered as 1 fractionated dose of AP-PA02 or placebo (1 dose distributed over 2 administrations given 6 hours apart on the same day on Day 1 and 10-12 hours apart each day on the remaining days) for 10 consecutive days. Subjects will administer AP-PA02 or placebo at home on days they do not visit the clinic. AP-PA02 and placebo will be administered in the clinic during Visit 1/Day 1 (both doses), Visit 2/Day 5 (morning dose only), and Visit 3/Day 10 (morning dose only).
q. The subject's current antipseudomonal inhaled antibiotic will be administered at Baseline, and for a total of 28 days, 10 days of study treatment and the following 18 days, for subjects in Cohort B only.
r. Only SAEs will be recorded from Screening until the first dose of AP-PA02 or placebo. After the first dose of AP-PA02 or placebo all AEs will be recorded.

AE = adverse event; CFU = colony-forming units; CT = computerized tomography; d = days; ECG = electrocardiogram; EOS = End of Study; ET = Early Termination; FEF_{25-75} = forced expiratory flow between 25% and 75% of the forced vital capacity; FEV_1 = forced expiratory volume; FVC = forced vital capacity; GLI = Global Lung Initiative;HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRCT = high-resolution computerized tomography; LCQ = Leicester Cough Questionnaire; QOL-B = Quality of Life-Bronchiectasis; RNA = ribonucleic acid; SAE = serious adverse event; SpO_2 = oxygen saturation; U = Unscheduled.

Table 2. Timing of Sample Collection and Procedures for the Treatment Period

	Treatment Period								
Visit	**1**				**2**		**3**		
Day	**1**				**5**		**10**		
Time	**Prior to first dose**	**30 minutes after first dose**	**1 hour after first dose**	**1 hour after second dose**	**Prior to first dose**	**30 minutes after first dose**	**Prior to first dose**	**30 minutes after first dose**	**1 hour after first dose**
Induced sputum sample (required)				*	*				*
Sputum culture					X				X
Sputum phage titer				X	X				X
Biomarkers				X	X				X
Expectorated sputum sample (if able to provide)					*		*		
Sputum culture					X		X		
Blood phage titer				X	X				X
Urinalysis					X		X		
Vital signs and SpO_2[a]	X	X		X	X	X	X	X	
Spirometry[b]	X			X	X		X		X
12-lead ECG	X		X						
Clinical laboratory assessments[c]	X				X		X		

a. Vital signs include blood pressure, heart rate, respiratory rate, and body temperature.
b. FEV_1, FVC, and FEF_{25-75} will be collected. Actual liter values will be recorded.
c. Includes clinical chemistry, hematology, and coagulation. See Appendix B for a list of clinical laboratory analytes.

d = days; ECG = electrocardiogram; EOS = End of Study; ET = Early Termination; FEF_{25-75} = forced expiratory flow between 25% and 75% of the forced vital capacity; FEV_1 = forced expiratory volume; FVC = forced vital capacity; SpO_2 = oxygen saturation.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Creatinine clearance [1]
Estimated glomerular filtration rate	Gamma-glutamyl transferase
Glucose	Inorganic phosphorus
Lactate dehydrogenase	Lipase
Potassium	Sodium
Total bilirubin	Total protein
Uric acid	

1. Creatinine clearance will be calculated using the Cockcroft-Gault equation based on actual body weight.

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential [1]	

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Coagulation

International Normalized Ratio

Pregnancy Test

Serum β-human chorionic gonadotropin [1]	Urine β-human chorionic gonadotropin [1]

1. For women of childbearing potential only, a serum pregnancy test will be performed during the Screening Period and a urine pregnancy test will be performed at the other visits.

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

1. Microscopy is performed only as needed based on abnormal dipstick test results.

Immunogenicity Test

Anti-phage antibody titer

Serology

Hepatitis B surface antigen

Hepatitis C virus by ribonucleic acid

Human immunodeficiency virus antibody

Biomarker Test

Sputum neutrophil elastase