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Statistical Analysis Plan for Interventional Studies

Text only

Sponsor Name: Armata Pharmaceuticals, Inc.

Protocol Number: AP-PA02-201
Protocol 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 Version and Date: 5.0 (19-Dec-2023)

[redacted]

Authors: [redacted]

Notice of Confidential and Proprietary Information:

Revision History

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1.0	28-May-2024	[redacted]	Initial Release Version

I confirm that I have reviewed this document and agree with the content.

Approvals

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Armata Pharmaceuticals, Inc. Approval

Mina Pastagia, MD, Chief Medical Officer	Mina Pastagia	*Electronically signed by: Mina Pastagia Reason: I am the approver Date: Jun 5, 2024 13:12 PDT*	Jun 5, 2024
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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass index
bpm	beats per minute
C	Celsius
CBC	complete blood count
CFU	colony-forming units
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FEF_{25-75}	Forced Expiratory Flow between 25 and 75% of the FVC
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GLI	Global Lung Function Initiative
ICH	International Conference on Harmonization
kg	kilogram
L	liter
LCQ	Leicester Cough Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters of mercury
Pa, P. aeruginosa	Pseudomonas aeruginosa
PFU	plaque-forming unit
PT	Preferred term
QOL-B	Quality of Life Bronchiectasis Questionnaire
QTc	corrected QT interval
QTcB	corrected QT interval using Bazett's formula
QTcF	corrected QT interval using Fridericia's formula

Abbreviation	Description
RR	respiratory rate
SAP	Statistical Analysis Plan
SD	Standard Deviation
SGRQ	Saint George's Respiratory Questionnaire
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

This SAP is created based on Protocol Number AP-PA02-201 version 5.0, dated 19 December 2023. This SAP will outline the planned analyses by Syneos Health (SYNH) to support the completion of the Clinical Study Report (CSR). This SAP describes in detail the statistical methodology and the statistical analyses to be conducted for the above-mentioned protocol. The planned analyses identified in this SAP follow the Statistical Principles for Clinical Trials such as International Council for Harmonisation (ICH) guidelines, E4 and E9.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all SDTM datasets, ADaM datasets and the tables, figures and listings used for the Data Safety Monitoring Board (DSMB) reports and the Clinical Study Report (CSR).

2.2. Timings of Analyses

The primary analysis of safety and efficacy is planned after all subjects complete the final study visit or terminate early from the study. Unless otherwise specified, the analysis includes all data collected in the study through to the time of database lock.

No formal interim analyses for efficacy or futility are planned.

Periodic safety evaluations will be performed by the DSMB, which 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 Armata. 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.

3. Study Objectives

3.1. Primary 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.

4. Study Details/Design

4.1. Brief Description

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

The study will evaluate AP-PA02 administered by inhalation in medically stable Non-Cystic Fibrosis Bronchiectasis (NCFB) subjects with chronic pulmonary *P. aeruginosa* infection at the time of Screening. A total of approximately 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 approximately 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 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 fractioned 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 treatment 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 day of treatment.

For Cohort B, eligible subjects will be randomized at the Baseline Visit to receive 1 fractioned 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 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 treatment 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 day of treatment.

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.

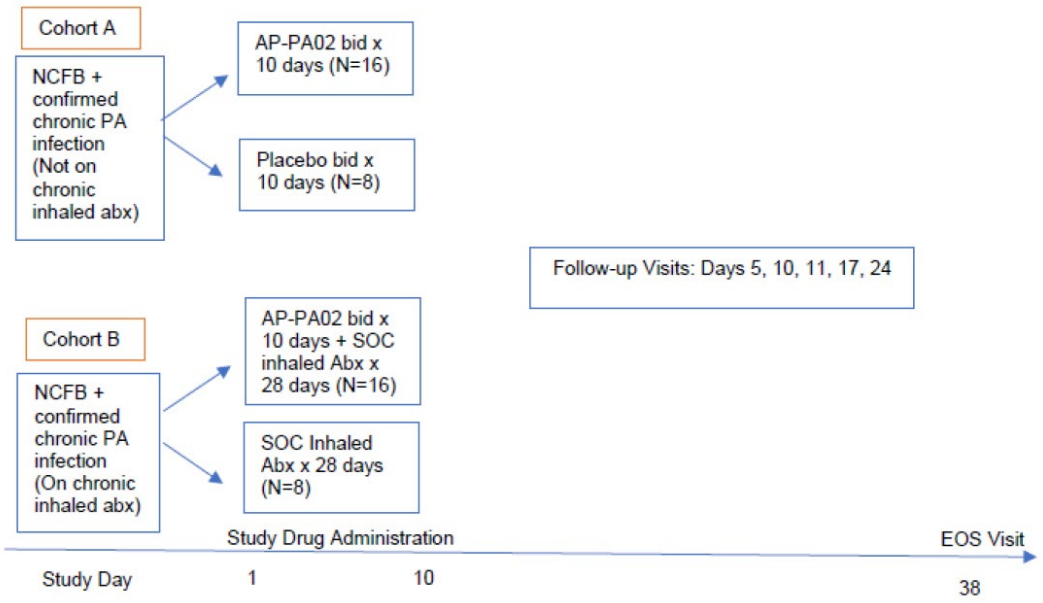
Safety evaluations after the first dose for each cohort will include vital signs (blood pressure, HR, RR [respiratory rate], and body temperature), SpO2, 12-lead Electrocardiogram (ECG), and spirometry. The schedule of subsequent assessments during and after treatment is detailed in the Schedule of Assessments.

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 4.1 displays the enrollment schematic.

Figure 4.1 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.

4.2. Subject Selection

Medically stable NCFB subjects with chronic pulmonary *P. aeruginosa* infection at the time of Screening who meet all inclusion and exclusion criteria will be eligible for participation in this study. The full list of inclusion and exclusion criteria is provided in Sections 4.2.1 and 4.2.2 below.

4.2.1. Inclusion Criteria

Inclusion Criteria are specified in the study protocol, Section 4.1.

4.2.2. Exclusion Criteria

Exclusion Criteria are specified in the study protocol, Section 4.2.

4.3. Determination of Sample Size

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 approximately 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 approximately 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.

4.4. Treatment Assignment and Blinding

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. Cohort A and Cohort B will be run in parallel. The maximum study treatment duration will be 10 days for Cohort A and Cohort B.

A total of approximately 24 eligible subjects will be randomized to Cohort A at the Baseline Visit to receive 1 fractionated dose of either AP-PA02 or placebo (2:1 ratio) administered via inhalation. The first 2 subjects in Cohort A 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.

A total of approximately 24 eligible subjects will be randomized to Cohort B at the Baseline Visit to receive 1 fractionated dose of either AP-PA02 plus their current antipseudomonal inhaled antibiotic or placebo plus their current antipseudomonal inhaled antibiotic (2:1 ratio) administered via inhalation. The first 2 subjects in Cohort 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.

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. The maximum study treatment duration for the optional cohorts will be up to 28 days.

Unblinding will occur after database lock to produce final results. In addition, unblinded DSMB members will have access to unblinded data for each DSMB meeting to produce the unblinded DSMB report. The Unblinded Syneos statistician will be responsible for providing the unblinded TLFs to the DSMB.

4.5. Administration of Study Medication

[redacted].

AP-PA02 will be administered in the clinic [redacted] 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.

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 treatment administration until he/she or the caregiver is comfortable with proper treatment 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. 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 treatment plus an additional 18 days). Subjects in Cohort B will also have 28 days of follow-up after the last day of treatment.

4.6. Study Procedures

Study procedures will follow the Schedule of Assessments (Study Protocol Appendix A, Table 1) and Timing of Sample Collection and Procedures for the Treatment Period (Study Protocol Appendix A, Table 2).

5. Endpoints

5.1. Primary Efficacy Endpoint

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

5.2. Secondary Efficacy Endpoints

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

5.3. Exploratory Efficacy Endpoints

The exploratory endpoints include the following:

- Anti-Pseudomonas 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 induced 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.

6. Analysis Sets

Subjects who enrolled prior to the first DSMB meeting and received AP-PA02 were given a lower dose (3 x 10^{11} PFU/day) of AP-PA02. After the first DSMB meeting, a decision was made to increase the dosage of AP-PA02 to 6 x 10^{11} PFU/day (see Section 8.5). Unless noted otherwise, summary outputs by treatment groups will exclude subjects who were enrolled on the study prior to the first DSMB meeting that occurred on 01Nov2023 and received AP-PA02.

Subjects who were enrolled on the study prior to the first DSMB meeting but received placebo will be 'pooled' with the subjects who were enrolled after the first DSMB meeting as the 'pooled' placebo group within their respective cohorts.

All subjects will be included in the listings.

6.1. Safety Population

The Safety Population will include all subjects who receive any AP-PA02 or placebo. Subjects will be analyzed according to treatment received. The Safety Population will be used for all analyses of safety endpoints and for the presentation of subjects in all subject listings including subject disposition.

6.2. 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 non-zero Baseline measurement and 1 post-Baseline assessment for the primary efficacy endpoint. In addition, subjects with any major protocol violations that could influence the validity of the data for the primary efficacy evaluation will be excluded. All criteria to exclude subjects from the Exploratory Efficacy Population will be made based on a blinded review of the data prior to the unblinding of the study.

6.3. 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 induced sputum, blood, or urine samples.

7. General Aspects for Statistical Analysis

7.1. General Methods

All analyses and summaries will be produced using Statistical Analysis System (SAS®) version 9.4 or higher. All SAS programs used to generate analytical results will be developed and validated according to [redacted] and SAS validation procedures. Summaries will be presented by treatment group unless otherwise specified.

Unless otherwise noted, continuous variables will be summarized using the number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), median, minimum, and maximum values as summary statistics. The minimum and maximum will be displayed to the precision with which the data were collected. The mean, median, and quartiles will be displayed to one additional decimal place and the SD will be displayed to two additional decimal places, where applicable.

Descriptive statistics for categorical/qualitative data will include frequency counts and percentages. The total number of subjects with a non-missing value for the given variable will be used as the denominator for percent calculations, unless stated otherwise. All percentages will be presented with one decimal, unless otherwise specified. Percentages equal to 100 will be presented as 100, and percentages will not be presented for zero frequencies.

All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings. Prior to database lock, the study statistician, data management lead, and medical monitor will review the data entered in the EDC to ensure that the database value falls within reasonable human measurements.

7.2. Key Definitions

7.2.1. Baseline

Unless otherwise specified, baseline is defined as the last non-missing observation prior to the first dose of AP-PA02 or placebo. If time is not collected for an assessment, baseline will be defined as the last non-missing observation on or prior to the first dose date of AP-PA02 or placebo. Assessments conducted on the nominal Baseline visit may not necessarily be flagged as the analysis baseline value.

7.2.2. Study Day

The day of first dose of treatment administration is defined as study Day 1. Subsequent days are numbered consecutively (Day 2, Day 3, etc.). Prior to the day of first dose of treatment administration, study days are numbered sequentially with negative values (i.e., Day -1, Day -2, etc.). There is no Day 0.

7.2.3. End of Study (EOS)

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 attending the EOS who require further follow-up may be entered into a separate long-term follow-up study.

7.3. Missing Data

In general, missing endpoint data will not be imputed. All analyses will be based on observed endpoints and related data. Sections 7.3.1 and 7.3.2 note the situations where missing data will be imputed.

7.3.1. Handling of Missing Dates/Months/Years for Prior/Concomitant Therapies

If the medication cannot be classified into concomitant or prior status due to incomplete start and/or stop date, the rules below will be applied for the classification.

For start date,

- If the year and month are observed but the day is missing, the first day of the month will be used unless month and year are the same as month and year of first dose date then impute using the day of first dose date.
- If the year is observed but the month and day are missing, the first day of the year, 01 Jan, will be used unless year is the same as first dose date then the first dose date will be used.
- If the start date is completely missing, the medication will be considered concomitant unless the stop date is before treatment administration.
- If the start and stop dates are both completely missing, a therapy will be considered concomitant.

For end date,

- If the year and month are observed but the day is missing, the last day of the month will be used unless month and year are the same as month and year of last dose date, then impute the last dose date.
- If the year is observed but the month and day are missing, the last day of the year, 31 Dec, will be used unless year is the same as last dose date then the last dose date will be used.
- If the end date is completely missing, if medication is still ongoing, then missing end date is not supposed to be imputed. If the medication is not ongoing and the start date is prior to first dose date, the end date will be imputed using 1st dose date.
- If both start and end dates are completely missing, medication will be considered concomitant.

The original partial or missing date will be shown in listings for all prior and concomitant medications.

7.3.2. Adverse Events Dates

For AEs with incomplete dates, the following rules will be used to impute start and/or stop dates for the sole purpose of determining if an AE is treatment emergent. Imputed dates will not appear in the data listings.

For partial start dates:

- If the month and year of AE onset are provided but day is missing
  - If the month and year match the month and the year of the date of first dosing administration, then the date of first dosing administration will be used and the AE will be considered treatment emergent.
  - Otherwise, the first day of the month will be used.
- If the year of AE onset is provided, but the month and day are missing
  - If the year matches the year of the first dosing administration, then the date of first dosing administration will be used.
  - Otherwise, 01 Jan will be used.
  - If the stop date is not missing and the imputed onset date is after the stop date, then the stop date will be used.
  - If the onset date is completely missing and the stop date is on or after the date of first dose, the event will be considered a treatment emergent adverse event (TEAE).

If both onset date and stop date are missing, the event will be considered a TEAE. Partial stop dates will not be imputed in this instance.

7.4. Visit Windows

There will be no derivation for visit windows in terms of summary assessments. Nominal visits will be used for by-visit tables.

For data with repeated observations at a given visit (e.g., laboratory assessments), the earliest of the available non-missing values at a visit should be used in summary tables. Other observations will be considered as unscheduled visits. For the purpose of tabulations, the unscheduled post-baseline values generally will be excluded from summary tables but will be included in the listing. Unscheduled visits will be considered for analyses of worst Common Terminology Criteria for Adverse Events (CTCAE) laboratory grades.

7.5. Pooling of Centers

Data from all sites will be summarized together for analyses.

7.6. Subgroups

No subgroup analyses are planned for this study.

However, a few key summary analyses may be repeated to include subjects who received AP-PA02 and were dosed prior to the first DSMB meeting as a sensitivity analysis.

8. Demographic, Other Baseline Characteristics and Medication

8.1. Subject Disposition and Withdrawals

A summary table will be produced detailing the number of subjects screened and screen failed, the number and percentage of all subjects in each analysis population, subjects who completed or discontinued study treatment, subjects who completed or who prematurely discontinued the study. In addition, reasons leading to discontinuation from study and study treatment discontinuation will be summarized for each cohort and overall. A listing of subject disposition will also be provided.

Screened subjects are defined as all subjects with a non-missing informed consent date and screen failures are defined as all subjects who sign the informed consent but are not enrolled into the study.

8.2. Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by each cohort and overall, for the Safety Population. The demographic data includes: age at screening (in years), sex at birth, race, ethnicity/geographic origin (North East Asian or South East Asian), height (cm), weight (kg), BMI (kg/m^2), and for females, childbearing potential. Baseline disease characteristics include forced expiratory volume [FEV_1 (L)], forced expiratory volume (FEV_1) % Predicted, forced vital capacity [FVC (L)], forced expiratory flow between 25 and 75% of the FVC [FEF_{25-75} (L)], Quality of Life Bronchiectasis (QOL-B) scale scores, Leicester Cough Questionnaire (LCQ) score, and Saint George's Respiratory Questionnaire (SGRQ) score.

Height (in m) = height (in cm) / 100

BMI (kg/m^2) = Weight(kg)/[Height$(m)^2$]

Demographics and Baseline characteristics will be listed by subject for the Safety Population.

8.3. Medical History

Medical History will be summarized for the Safety Population using Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The reported medical history terms will be coded using MedDRA Version 25.0 or higher. The number of subjects with any medical or surgical history will also be summarized. A subject experiencing a medical history within more than one SOC and PT will be counted only once within that SOC and PT, respectively.

Medical history findings will be listed by subject using the Safety Population.

8.4. Medication

Medications used within 30 days prior to Screening will be recorded.

All prior and concomitant medications will be classified using the anatomical Therapeutic Chemical (ATC) classification codes and preferred drug names from the World Health Organization Drug Dictionary (WHO-DD), March 2022.

Summaries of prior and concomitant medications will be presented separately in tabular form using the ATC 4 level term as an upper classification level and the preferred drug name as a lower classification level. If the medication does not have an ATC level 4 term, the ATC level 3 term is used. If the ATC level 3 term is also unavailable, the ATC level 2 term is used. All medications will be summarized by

descending frequency of ATC level 4 and preferred drug name within a given ATC level 4 term. The summary will consist of the frequency and percent of safety subjects who used the medication at least once.

For each subject, the medication will be counted only once within a level 4 ATC and only once within a given preferred drug name level. A subject may appear more than once if he/she has more than one concomitant medication coded under different ATC categories; however, the subject will be counted only once in the overall category.

A by-subject listing with coded terms will also be provided along with calculated study day.

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.

8.4.1. Prior Medication

Any medication that started prior and did not continue past the first dose of study treatment will be classified as prior.

8.4.2. Concomitant Medication

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 electronic case report form (eCRF). All medications taken during the study treatment period, including those which started before study treatment but continued past or started on or after the first dose date of study treatment, will be classified as concomitant.

8.5. Extent of Exposure

[redacted]

Prior to the first DSMB meeting, the AP-PA02 dose was 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.

After the first DSMB meeting, the dose was doubled.

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 [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.

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 treatment. 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 treatment plus an additional 18 days).

Treatment exposure will be summarized using the treatment duration (days), total dose administration time (minutes), and number of doses for the Safety Population. Treatment duration is the number of days between first and last treatment inhalation, defined as the last inhalation date – first inhalation date + 1. Dose administration time is the elapsed time between start time and stop time of treatment administration, defined as stop time (HH:MM) – start time (HH:MM), and will include dose interruption or delay, if any occurred. Total dose administration time will be calculated utilizing the time of administration from only the first dose of each day and then summing these times over the total treatment duration. Continuous variables will be summarized with descriptive statistics of mean, SD, median, minimum, and maximum.

8.6. Treatment Compliance

Details of the date and time when the treatment is administered, along with any deviation from the procedure described in the Protocol, will be recorded in the subject's source documents and the eCRF. For the days subjects administer treatment 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 treatment. Compliance for both clinic and home administration of treatment will be displayed in a data listing.

Treatment compliance will be summarized using the following parameter based on the data collected in the EDC:

- *Percent Compliance*, calculated as the total number of study drug administrations divided by total number of expected study drug administrations x 100. The total number of expected study drug administrations will be 20 for subjects who complete up to Day 10/Visit 3. For subjects who discontinued prior to Day 10/Visit 3, the total number of expected study drug administrations will be calculated as the last non-zero treatment administration study day during the treatment period x 2. For example, a subject who discontinued prior to Day 10/Visit 3 had his/her last non-zero study drug administration on study day 7, the total number of expected study drug administrations will be 14.

The above parameter will be summarized for each treatment group, for subjects in the Safety Population.

8.7. Protocol Deviations

In the event of a major protocol deviation, the Investigator and Sponsor's Medical Monitor and/or designee will determine whether the subject should continue to participate in the study. The Investigator should notify the IRB/IEC of deviations from the protocol or SAEs occurring at the site.

Protocol deviation management is detailed in the Protocol Deviation and Non-compliance Management Plan.

A data listing of all protocol deviations will also be provided.

9. Efficacy

All efficacy analyses will be performed using the Exploratory Efficacy Population unless specified otherwise. Subjects will be analyzed by cohort as members of the treatment group to which they were randomized.

9.1. Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint is change from baseline in *P. aeruginosa* density (CFU/mL) as measured in induced sputum samples at 1 week after end of treatment (Visit 5/Day 17). The endpoint will be analyzed as logarithmic colony-forming units/mL sputum based on the Exploratory Efficacy Population (i.e., CFU counts will be transformed on a log10 scale prior to analysis and the calculation of change from baseline).

Cohort A and Cohort B will be analyzed independently. As there is no adjustment for multiple hypothesis testing only 95% confidence intervals comparing the two treatment groups will be calculated using a 2-sample t test with 0.05 significance level. No p-values will be calculated.

The following data will be excluded from the analysis:

- Data with missing *P. aeruginosa* density count.
- Data with qualitative results (i.e., not quantitative results) due to poor specimen quality.
- Data with specimen condition

A subject may have results from multiple isolates per timepoint. In such cases, *P. aeruginosa* density will be calculated as the sum of *P. aeruginosa* density from multiple isolates per subject per timepoint. Expectorated sputum sample data will not be used for analysis, but the data will be provided in a by-subject listing.

9.2. Exploratory Endpoints and Analyses

9.2.1. Anti-Pseudomonas antibiotic sensitivity of *P. aeruginosa* isolates at specified time points during the study

This analysis will be described in a separate plan.

9.2.2. Change in *P. aeruginosa* density from Baseline

Induced sputum culture will be collected as indicated in the Schedule of Assessments in Table 1 of the Protocol Appendix A . Change and percent change in *P. aeruginosa* density (CFU/mL) from induced sputum from Baseline through EOS will be summarized using descriptive statistics at each scheduled time point and will be presented by treatment group. *P. aeruginosa* density count data will be transformed on a log10 scale prior to analysis; summary statistics will display results on the transformed values.

The following data will be excluded from the analysis:

- Data with missing P. aeruginosa density count.
- Data with qualitative results (i.e., not quantitative results) due to poor specimen quality.
- Data with specimen condition

In addition to the descriptive summary statistics, figures of *P. aeruginosa* mean density (in original scale and log10 scale) versus time will be developed for each cohort.

By subject plot of *P. aeruginosa* density (in original and log10 scale) in induced sputum samples over time will also be developed.

9.2.3. Change in spirometry from Baseline

Spirometry analyses are described Section 10.3 of this SAP.

9.2.4. Change from Baseline levels of induced sputum neutrophil elastase

Biomarkers, including induced sputum neutrophil elastase, will be collected at all study visits from Baseline through EOS and tested by the central laboratory. Change from Baseline through EOS will be summarized using descriptive statistics at each scheduled time point and will be presented by treatment group. Subjects with a missing value at Baseline or post Baseline will not be included in the summary from change from Baseline.

9.2.5. Change in quality of life as assessed by the Quality of Life-Bronchiectasis (QOL-B) Questionnaire

The QOL-B Questionnaire is a self-administered PRO measure designed specifically for subjects with bronchiectasis[1], and will be self-administered at Baseline, Visit 4/Day 11, and Visit 6/Day 24. This PRO contains 37 items on 8 scales: Respiratory Symptoms, Physical, Role, Emotional and Social Functioning, Vitality, Health Perceptions, and Treatment Burden. Each of the 37 items are scored from 1-4, and each of the 8 scale scores are standardized on a 0-100 point scale with higher scores indicating fewer symptoms or better functioning and health related QOL. A total score is not calculated.

SAS programming code for calculating scores for the 8 scales is provided in Appendix 15.1. The scaled scores for each of the 8 scales and absolute change from Baseline will be summarized by visit using summary statistics for continuous variables by treatment group.

9.2.6. Change in quality of life as assessed by the Leicester Cough Questionnaire (LCQ)

The LCQ is a 19-item self-completed QOL measure of chronic cough with is responsive to change[2], and will be administered at Baseline, Visit 4/Day 11, and Visit 6/Day 24. The LCQ contains 19 items which assess three domains: physical (8 items), psychological (7 items), and social (4 items). Subjects will respond to each item using a 7-point Likert response scale.

Questions 1, 2, 3, 9, 10, 11, 14, and 15 comprise the physical domain; questions 4, 5, 6, 12, 13, 16, 17 comprise the psychological domain; and questions 7, 8, 18, 19 comprise the social domain. For each domain, scores are calculated by determining the mean for that domain (sum of scores from items in the domain / number of items in domain; range 1-7). Total LCQ scores are calculated by summing the domain scores (range 3-21).

Physical, psychological, and social domain scores and the Total LCQ score, as well as absolute change from Baseline, will be summarized by visit using summary statistics for continuous variables by treatment group.

9.2.7. Change in quality of life as assessed by the Saint George's Respiratory Questionnaire

The SGRQ is a measure to assess impaired health and perceived well-being (quality of life)[3] and will be administered at Baseline and Visit 7 EOS/Day 38. This 14-question questionnaire (40 total items; some questions have multiple items) has 2 parts: Part 1 (questions 1-7) generates the symptom component score, while Part 2 (questions 8-14) generates the activity and impact component scores.[4,5] A total SGRQ score

is also generated. Each possible response to each of the 14 questions is assigned a weight (range 0-100) (Appendix 15.2).

The SGRQ is scored in 2 steps:

- Step 1: Sum weights for all items with a positive response. A positive response is one that shows the presence of symptoms. For example, in Part 1 Question 1, all answers ("Most days a week", "Several days a week" and "Only with respiratory infections") except "Not at all" would be positive. A positive response also has a nonzero score, unlike a negative one. For Part 2 Question 8 ("How would you describe your respiratory problems?"), the following responses are positive: "Cause me a lot of problems or are the most important physical problems I have", "Causes me a few problems"; an answer of "Causes no problem" is negative as it does not show any signs of symptoms. For Part 2 Question 14, any answer except "They do not stop me from doing anything I would like to do" would be considered positive.
    - The symptom component score is calculated by summing weights for questions 1 through 7.
    - The activity component score is calculated by summing weights for positive responses to questions 9 and 12.
    - The impact component score is calculated by summing weights for questions 8, 10, 11, 13, and 14. Note that weights for positive responses to questions 10, 11, and 13 are summed with the response to the single item selected for questions 8 and 14.
- Step 2: Calculate component scores and total score.
    - The score for each component is calculated separately by dividing the summed weights by the maximum possible summed weights for that component and expressing the result as a percentage.

      *Score = 100 * (summed weights from all positive items in that component / sum of maximum weights for all items in that component)*
    - The total score is calculated by dividing the summed weights for all questions by the maximum possible sum of weights and expressing the result as a percentage.

      *Score = 100 * (summed weights from all positive items in SGRQ / sum of maximum weights for all items in SGRQ)*

A total score can be calculated in the presence of missing data, but only if the domains meet the following "missing items" rule. If one domain exceeds its permitted number of missed items, then a total score cannot be calculated.

"Missing items" rules are as follows:

- Symptoms (Questions 1-7)

  The symptom component will tolerate a maximum of 1 missed item. The weight for the missed item is subtracted from the total possible weight for the symptom component (566.2) and from the Total weight (3201.9).

- Activity (Questions 9, 12; this component has 13 items)

  The Activity component will tolerate a maximum of 3 missed items. The weight for the missed item is subtracted from the total possible weight for the Activity component (982.9) and from the Total weight (3201.9).

- Impacts (Questions 8, 10, 11, 13, 14; this component has 20 items)

  The Impacts component will tolerate a maximum of 5 missed items. The weight for the missed item is subtracted from the total possible weight for the Impacts component (1652.8) and from the Total weight (3201.9).

Symptom, activity, and impact component scores and the Total score, as well as absolute change from Baseline, will be summarized using summary statistics for continuous variables by treatment group.

10. Pharmacokinetics

Pharmacokinetics analyses will be described in a separate plan.

11. Safety

The population used for safety analyses will be the Safety Population. Safety will be assessed on the basis of treatment-emergent adverse event (TEAE), vital signs, laboratory assessments, immunogenicity, ECG parameters, and physical examinations.

All safety information will be provided in subject listings.

11.1. Adverse Events / Adverse Drug Reactions

An overall summary of TEAEs will be provided by treatment group and overall, including the number and percentage of subjects who experience at least one of the following:

- TEAEs
- Serious TEAEs
- TEAEs related to study drug
- TEAEs related to study device
- TEAEs related to study procedure
- Serious TEAEs related to study drug
- Serious TEAEs related to study device
- Serious TEAEs related to study procedure
- TEAEs leading to permanent withdrawal of study drug
- TEAEs related to study drug leading to permanent withdrawal of study drug
- TEAEs with Grade 1 (Mild) as Worst Severity
- TEAEs with Grade 2 (Moderate) as Worst Severity
- TEAEs with Grade 3 (Severe) as Worst Severity
- TEAEs with Grade 4 (Life-Threatening) as Worst Severity
- TEAEs leading to death

The number and incidence of events will be provided in the overall summary table by treatment group and overall.

TEAE is defined as an adverse event that was not present prior to administration of the first dose of study drug and subsequently presented after the first dose, or any exacerbation occurring after first dose of an event that was present prior to the first dose.

All AEs will be listed by subject and chronologically by date of AE onset, and by study part, dose group, and subject. The listing will include all data collected in the eCRF and the coded variables. AE dates will be listed as recorded in the eCRF. AEs will be classified by System Organ Class (SOC) and Preferred Term (PT) using MedDRA Version 25.0. Subjects are counted only once within each SOC and PT. TEAEs will be presented by descending frequency by SOC and PT.

Further, the following TEAE summaries will be provided and summarized by treatment group and overall:

- Any TEAEs overall and by SOC and PT
- Serious TEAEs, overall and by SOC and PT
- Study Drug-related TEAEs overall and by SOC and PT
- Study Device-related TEAEs overall and by SOC and PT
- Study Procedure-related TEAEs overall and by SOC and PT

- Serious TEAEs related to Study Drug, overall and by SOC and PT
- Serious TEAEs related to Study Device, overall and by SOC and PT
- Serious TEAEs related to Study Procedure, overall and by SOC and PT
- TEAEs by worst severity, overall and by SOC and PT
- Study Drug-related TEAEs by maximum severity, overall and by SOC and PT
- Study Device-related TEAEs by maximum severity, overall and by SOC and PT
- Study Procedure-related TEAEs by maximum severity, overall and by SOC and PT
- TEAEs leading to permanent withdrawal of study drug, overall and by SOC and PT
- Study Drug-related TEAEs leading to permanent withdrawal of study drug, overall and by SOC and PT
- Study Device -related TEAEs leading to permanent withdrawal of study drug, overall and by SOC and PT
- Study Procedure -related TEAEs leading to permanent withdrawal of study drug, overall and by SOC and PT
- TEAEs which resulted in death, overall and by SOC and PT

If a subject has more than one event within a given SOC or PT at different severities, the maximum severity will be tabulated. For example, if a subject experiences two events with the same preferred term, but one was at moderate and the other at severe severity, the severe TEAE will be included in the tabulation. Severity is classified into five categories: mild, moderate, severe, life-threatening, and death.

An AE will be considered drug-related if the relationship attribution is ‘possibly related’, ‘probably related’, or ‘definitely related’ or designation is missing. AEs with a missing onset date, but with stop date either missing or on or after the date of first dose of study drug will be included as treatment emergent. All AEs will be listed in subject listing and summarized by numbers and percent of subjects by dose for each portion of the study separately. If a subject reports the occurrence of a particular event more than once, the most severe of those events will be included in the summary tables of TEAEs, and the most severe of the treatment-related events will be included in the summary tables of treatment-related events.

If the relationship to study drug, study device, or study procedure, is missing for an AE, the event will be assumed to have the maximum relationship (i.e., definitely), respectively. If the seriousness status is missing for an AE, the event will be assumed to be serious.

11.2. Anti-Phage Antibody Titer

The anti-phage antibody titer will be assessed as indicated in the Schedule of Assessments in Table 1 of the Protocol Appendix A. Immunogenicity sampling times and results will be listed for the Safety Population.

11.3. Spirometry

Spirometry assessments FEV_1, FVC, and FEF_{25-75} will be collected locally at the clinical study site. Actual liter values will be recorded. Details regarding spirometry procedures and standards will be included in the Study Manual. Spirometry will be assessed according to the Schedule of Assessments in Table 1 of the Protocol Appendix A and Timing of Sample Collection and Procedures for the Treatment Period in Table 2 of the Protocol Appendix A. Spirometry will be collected prior to sputum induction on non-Treatment Period Visits.

Observed values and mean changes from baseline will be presented for each spirometry parameter using descriptive statistics (i.e., n, mean, standard deviation, median, minimum, and maximum) by treatment group and visit, using the Safety population. If multiple measurements are to be performed at each time

point, the highest value will be used for analysis.

A by-subject listing will be provided, including each spirometry parameter, and will be sorted by subject and visit.

A by-subject line plot will be presented by spirometry parameter and cohort. Each cohort will be on a new plot, with all subjects of the same cohort on the same plot. Any unscheduled results will also be part of this plot.

The number and percentage of subjects with PCS values will be summarized by visit/timepoint and for any time post-baseline. Potentially clinically significant values will be identified for FEV_1 (forced expiratory volume) as outlined below.

Table 13.6.1 Potentially Clinically Significant Values for Forced Expiratory Volume Decrease

Parameter	Units	Criteria for PCS Values (Observed values)	
		High	Low
Forced Expiratory Volume	%	NA	70 – 99 60 – <70 50 – <60 <50

11.3.1. Change in FEV_1 from Baseline through End of Study

Forced Expiratory Volume in 1 second (FEV_1) (L) change from baseline and % Predicted FEV_1 change from baseline will be summarized by visit using summary statistics for continuous variables.

Percent predicted FEV_1 (%) will be calculated by implementing the Global Lungs Initiative 2012 regression equations. The predicted value of FEV_1 is a function of sex, age, height, and ethnicity and is of this form:

M = exp(a0 + a1·ln(Height) + a2·ln(Age) + a3·black + a4·NEAsia + a5·SEAsia + a6·Other + Mspline)

M = predicted value
Exp = exponential function
ln() = natural log transformation
black = 1 if a subject is Black or African American, otherwise = 0
NEAsia = 1 if a subject is from North East Asia, otherwise = 0
SEAsia = 1 if a subject is from South East Asia, otherwise = 0
Other = 1 if subject is 'other ethnic group' or mixed ethnicity (i.e., subject is not indicated to be from North East Asia, South East Asia, or African American from eCRF page 'Demographics'), otherwise = 0
coefficients a0… a6 depend on the measurement and gender
Mspline = age and sex varying coefficients provided by Qanjer PH, Stanojeciv S, Cole TF, et al.

The coefficients and Mspline values used for predicted FEV_1 calculations are provided in Appendix 15.3.

Finally, % predicted = (measured/M) * 100.

11.4. Clinical Laboratory Evaluations

Clinical laboratory measurements (chemistry, hematology, coagulation, and urinalysis) will be obtained at Screening, Baseline, and subsequent study visits according the Schedule of Assessments in Table 1 of the Protocol Appendix A, and will be summarized by treatment group in the following ways:

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

By-subject safety laboratory listings will be generated incorporating information and assessment results obtained from the designated laboratory which provided normal range and reported out of range results. All laboratory results in SI units will be presented in data listings. Tests will be listed in alphabetical order within their respective panels (standard safety chemistry, hematology, coagulation, and urinalysis).

Potentially clinically significant chemistry and hematology laboratory results will be summarized using severity grades according to NCI CTCAE (version 5.0 or higher) where applicable. The worst post-baseline severity grade will be summarized and is defined as the most severe toxicity grade of the specific parameter assessed during the study at a scheduled or unscheduled visit. If a severity grade scale is missing for a laboratory parameter, the normal ranges of the clinical laboratory will be used.

11.4.1. Chemistry

Serum chemistries will include alanine aminotransferase, albumin, alkaline phosphatase, amylase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, calcium, chloride, creatine kinase, creatinine, creatinine clearance, estimated glomerular filtration rate, gamma-glutamyl transferase, glucose, inorganic phosphorus, lactate dehydrogenase, lipase, potassium, sodium, total bilirubin, total protein, and uric acid. Creatinine clearance is to be calculated using the Cockcroft-Gault equation adjusted for actual body weight.

11.4.2. Hematology

Hematology will include a complete blood count (CBC), which includes hematocrit, hemoglobin, platelet count, red blood cell count, and white blood cell count and differential.

11.4.3. Coagulation

Coagulation testing will include international normalized ratio.

11.4.4. Urinalysis

Urinalysis will be performed at the local laboratory at time points designated in the Timing of Sample Collection and Procedures for the Treatment Period in Table 2 of the Protocol Appendix A. Urinalysis will be performed by visual inspection and dipstick, and will include bilirubin, blood, glucose, ketones, leukocyte esterase, microscopy, nitrite, pH, protein, specific gravity, and urobilinogen. In addition, microscopy will be performed only as needed based on abnormal dipstick test results.

11.5. Vital Signs

Vital sign measurements will consist of blood pressure (systolic and diastolic), oxygen saturation, heart rate, respiratory rate, and body temperature. Descriptive summaries (number of subjects, mean, standard deviation, median, minimum, and maximum) of actual values and changes from baseline will be presented for each visit and time point. These summaries will be presented for the safety population and by treatment group. Vital signs will be performed at all study visits at prespecified time points per the Timing of Sample Collection and Procedures for the Treatment Period in Table 2 of the Protocol Appendix A.

Temperature will be summarized in Celsius (C) units. Fahrenheit (F) will be converted to Celsius using the following conversion:

Temperature (in °C) = 5/9 (Temperature [in °F]-32)

Potentially clinically significant (PCS) vital sign abnormalities will be categorized based on Table 13.3.1 and summarized by treatment group and assessment visit.

Table 13.3.1 Potentially Clinically Significant Values for Vital Signs

Vital Sign Parameter	Units	Criteria for PCS Values (Observed values)		Criteria for PCS values (Change from Baseline values)	
		High	Low	Increase	Decrease
Heart rate (sitting)	Beats/min	>120	<40	NA	NA
Systolic Blood Pressure (sitting)	mmHg	>180	<90	≥30	≥30
Diastolic Blood pressure (sitting)	mmHg	>110	<50	≥20	≥20
Oxygen Saturation (sitting)	%	NA	<92	≥5	≥5

A by-subject line plot will be provided by treatment group. Vital sign data will be listed chronologically by subject and visit for each vital sign parameter.

11.6. Twelve-Lead Electrocardiograms

A 12-lead ECG will be performed locally at the site according to the Schedule of Assessments in Table 1 of the Protocol Appendix A and Timing of Sample Collection and Procedures for the Treatment Period in Table 2 of the Protocol Appendix A for all subjects. The Fridericia formula for calculating QTc will be used (i.e., QTcF).

A shift table of the Investigator's assessment of ECG results at each visit compared with baseline values will be presented by treatment group using the following categories: normal; abnormal (not clinically significant); abnormal (clinically significant). The number and percentage of subjects in each cross-classification group of the shift table will be presented by treatment group. Subjects with a missing value at baseline or post baseline will not be included in the denominator for percentage calculation.

A by-subject listing will be provided, including each ECG parameter: ventricular heart rate (beats per minute [bpm]), PR interval [msec], RR interval [msec], QRS Duration [msec], QT interval [msec], QTcB interval [msec], QTcF interval [msec], and Investigator's interpretation. Potentially clinically significant QTcF values will be flagged in the listing.

The number and percentage of subjects with PCS and potentially clinically significant change (PCSC) values will be summarized by visit/timepoint and for any time post-baseline. Potentially clinically significant values will be identified for ECG parameters as outlined below.

Table 13.4.1 Potentially Clinically Significant Values for QT and QTcF

ECG Parameter	Units	Criteria for PCS Values (Observed values)		Criteria for PCS values (Change from Baseline values)	
		High	Low	Increase	Decrease
QT, QTcF	msec	>450 but <=480 >480 but <=500 >500	NA	>=30 to 60 >60	NA

11.7. Physical Examinations

A full physical examination will be performed at Screening, Baseline, and the EOS visit. A symptom-directed physical examination will be performed at the other visits.

Physical examination results will be listed but not summarized.

11.8. 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 in Table 1 of the Protocol Appendix A. Pregnancy test results will be provided in a listing.

12. Interim Analyses

No formal interim analyses for efficacy or futility are planned. No formal interim report will be generated.

13. Changes from Analysis Planned in Protocol

Not applicable.

14. Reference List

1. Quittner AL, O'Donnell AE, Salathe MA, et al. Quality of Life Questionnaire Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. Thorax.2015;70(1):12-20.

2. Birring SS, Prudon B, Carr AJ, et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58(4):339-343.

3. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med. 1991;85 Suppl B:25-31; discussion 33-37.

4. Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis. 1992;145(6):1321-1327.

5. Jones, P. (2016, March). Retrieved from https://www.sgul.ac.uk/research/research-operations/research-administration/st-georges-respiratory-questionnaire/docs/sgrq-c-manual-april-2012.pdf.

6. Quellhorst L, Barten G, de Roux A, et al. Psychometric Validation of the German Translation of the Quality of Life Questionnaire Bronchiectasis (QOL-B) – Data from the German Bronchiectasis Registry PROGNOSIS. J Clin Med. 2022; 11(2): 441.

7. Qanjer PH, Stanojeciv S, Cole TF, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. European Respiratory Journal. 2012.

8. Qanjer PH, Stanojeciv S, Cole TF, et al. Quanjer GLI-2012 Regression Equation and Lookup Tables. Global Lung Function Initiative

15. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures, or statistical analyses. [redacted] Standard Operation Procedures (SOPs) Developing Statistical Programming and Validation Plan [redacted], End-to-End Process of the Production of Study Data Tabulation Model (SDTM) [redacted], and End-to-End Process of the Production of Analysis Datasets (ADaM) and Tables, Figures, and Listings [redacted] describe the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

16. Appendices

16.1. SAS Programming Code for Scoring the QoL-B

/*This scoring program requires that the data be imported into a SAS table titled "QOLB"
and that the variable names in the table match those listed below.[6]*/

```
data QOLB; set QOLB;

/* Rescaling Respiratory 32 */
if resp32=6 then resp32=.;
  else if resp32=1 then resp32= 4;
  else if resp32=2 then resp32= 3;
  else if resp32=3 then resp32= 2;
  else if resp32=4 then resp32= 1;
  else if resp32=5 then resp32= 1;

/* Rescaling “doesn’t apply” Social 19 */
if social19=5 then social19=.;

/* Recoding Some Variables */
health5=5-health5;
vital8=5-vital8;
treat12=5-treat12;
treat14=5-treat14;
health15=5-health15;
role20=5-role20;
health24=5-health24;
role27=5-role27;
run;

/* Calculating Scores */
data QOLB; set QOLB;

if nmiss (phys1, phys2, phys3, phys4, phys16) <= 2 then
  physical = (mean (phys1, phys2, phys3, phys4, phys16)-1)/3*100;
if nmiss (role17, role20, role25, role27, role28) <= 2 then
  role = (mean (role17, role20, role25, role27, role28)-1)/3*100;
if nmiss (vital6, vital8, vital9) <= 1 then
  vitality = (mean (vital6, vital8, vital9)-1)/3*100;
if nmiss (emot7, emot10, emot11, emot23) <= 2 then
  emotion = (mean (emot7, emot10, emot11, emot23)-1)/3*100;
if nmiss (social18, social19, social22, social26) <= 2 then
  social = (mean (social18, social19, social22, social26)-1)/3*100;
if nmiss (treat12, treat13, treat14) <= 1 then
  treat = (mean (treat12, treat13, treat14)-1)/3*100;
if nmiss (health5, health15, health21, health24) <= 2 then
  health = (mean (health5, health15, health21, health24)-1)/3*100;
if nmiss (resp29, resp30, resp31, resp32, resp33, resp34, resp35, resp36, resp37) <= 4 then
  respirat = (mean (resp29, resp30, resp31, resp32, resp33, resp34, resp35, resp36, resp37)-1)/3*100;
run;
```

16.2. Saint George's Respiratory Questionnaire Scoring Weights

Saint George's Respiratory Questionnaire Scoring Weights[5]		
Question	Answers	Weight
Part 1		
Question 1: I cough	Most days a week	80.6
	Several days a week	46.3
	Only with respiratory infections	28.1
	Not at all	0.0
Question 2: I bring up phlegm (sputum)	Most days a week	76.8
	Several days a week	47.0
	Only with respiratory infections	30.2
	Not at all	0.0
Question 3: I have shortness of breath	Most days a week	87.2
	Several days a week	50.3
	Not at all	0.0
Question 4: I have attacks of wheezing	Most days a week	86.2
	Several days a week	71.0
	A few days a month	45.6
	Only with respiratory infections	36.4
	Not at all	0.0
Question 5: How many attacks of chest trouble did you have during the last year?	3 or more attacks	80.1
	1 or 2 attacks	52.3
	None	0.0
Question 6: How often do you have good days (with few respiratory problems)?	No good days	93.3
	A few good days	76.6
	Most days are good	38.5
	Every day is good	0.0
Question 7: If you have a wheeze, is it worse when you get up in the morning?	No	0.0
	Yes	62.0
Part 2		
Question 8: How would you describe your respiratory problems?	Cause me a lot of problems or are the most important physical problem I have	82.9
	Cause me a few problems	34.6
	Cause no problems	0.0
Question 9: Questions about what activities usually make you feel breathless. Note: this is a 5-item question	Washing or dressing yourself	82.8
	Walking around the house	80.2
	Walking outside on the level ground	81.4
	Walking up a flight of stairs	76.1
	Walking up hills	75.1
Question 10: Some more questions about your cough and breathlessness. Note: this is a 6-item question	Coughing hurts	81.1
	Coughing makes me tired	79.1
	I am short of breath when I talk	84.5
	I am short of breath when I bend over	76.8

	My cough or breathing disturbs my sleep	87.9
	I get exhausted easily	84.0
Question 11: Questions about other effects that your chest trouble may have on you. Note: this is a 7-item question	My cough or breathing is embarrassing in public	74.1
	My respiratory problems are a nuisance to my family, friends, or neighbors	79.1
	I get afraid or panic when I cannot catch my breath	87.7
	I feel that I am not in control of my respiratory problems	90.1
	I have become frail or an invalid because of my respiratory problems	89.9
	Exercise is not safe for me	75.7
	Everything seems too much of an effort	84.5
Question 12: These are questions about how your activities might be affected by your respiratory problems. Note: this is a 8-item question	I take a long time to get washed or dressed	74.2
	I cannot take a bath or shower, or I take a long time to do it	81.0
	I walk slower than other people, or I stop to rest	71.7
	Jobs such as house chores take a long time, or I have to stop to rest	70.6
	If I walk up one flight of stairs, I have to go slowly or stop	71.6
	If I hurry or walk fast, I have to stop or slow down	72.3
	My breathing makes it difficult to do things such as walk up hills, carry things up stairs, do light gardening such as weeding, dance, bowl, or play golf	74.5
	My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, job or walk briskly (5 miles per hour), play tennis, or swim	71.4
Question 13: We would like to know how your chest usually affects your daily life. Note: this is a 5-item question	I cannot play sports or do other physical activities	64.8
	I cannot go out for entertainment or recreation	79.8
	I cannot go out of the house to do the shopping	81.0
	I cannot do household chores	79.1
	I cannot move far from my bed or chair	94.0
Question 14: How do your respiratory problems affect you?	They do not stop me from doing anything I would like to do	0.0

	They stop me from doing one or two things I would like to do	42.0
	They stop me from doing most of the things I would like to do	84.2
	They stop me from doing everything I would like to do	96.7

16.3. Global Lung Function Initiative (GLI) Regression Coefficients

The linear coefficients used in conjunction with the Mspline values include the following:

Males:

Intercept	a0	-10.3420
Height	a1	2.2196
Age	a2	0.0574
Afr. Am.	a3	-0.1589
N East Asia	a4	-0.0351
S East Asia	a5	-0.0881
Other/mixed	a6	-0.0708
		Mspline

Females:

Intercept	a0	-9.6987
Height	a1	2.1211
Age	a2	-0.0270
Afr. Am.	a3	-0.1484
N East Asia	a4	-0.0149
S East Asia	a5	-0.1208
Other/mixed	a6	-0.0708
		Mspline

Mspline lookup values from Qanjer PH, Stanojeciv S, Cole TF, et al.:

Age	Mspline - Female	Mspline - Male
3	-0.2311	-0.1133
3.25	-0.2170	-0.1073
3.5	-0.2040	-0.1011
3.75	-0.1922	-0.0951
4	-0.1817	-0.0893
4.25	-0.1727	-0.0841
4.5	-0.1651	-0.0799
4.75	-0.1592	-0.0769
5	-0.1548	-0.0752
5.25	-0.1518	-0.0750
5.5	-0.1494	-0.0758
5.75	-0.1474	-0.0771
6	-0.1452	-0.0787
6.25	-0.1426	-0.0803
6.5	-0.1393	-0.0816

6.75	-0.1354	-0.0823
7	-0.1310	-0.0822
7.25	-0.1264	-0.0815
7.5	-0.1217	-0.0804
7.75	-0.1171	-0.0792
8	-0.1125	-0.0778
8.25	-0.1076	-0.0763
8.5	-0.1022	-0.0745
8.75	-0.0963	-0.0721
9	-0.0897	-0.0691
9.25	-0.0825	-0.0658
9.5	-0.0747	-0.0622
9.75	-0.0663	-0.0586
10	-0.0573	-0.0549
10.25	-0.0479	-0.0513
10.5	-0.0380	-0.0476
10.75	-0.0278	-0.0437
11	-0.0172	-0.0395
11.25	-0.0063	-0.0350
11.5	0.0048	-0.0299
11.75	0.0161	-0.0241
12	0.0274	-0.0176
12.25	0.0386	-0.0101
12.5	0.0496	-0.0019
12.75	0.0604	0.0071
13	0.0709	0.0169
13.25	0.0810	0.0274
13.5	0.0907	0.0384
13.75	0.0999	0.0497
14	0.1086	0.0612
14.25	0.1168	0.0728
14.5	0.1244	0.0844
14.75	0.1315	0.0958
15	0.1379	0.1068
15.25	0.1438	0.1175
15.5	0.1492	0.1276
15.75	0.1540	0.1371
16	0.1583	0.1460
16.25	0.1621	0.1542
16.5	0.1655	0.1616

16.75	0.1684	0.1684
17	0.1711	0.1744
17.25	0.1733	0.1798
17.5	0.1753	0.1845
17.75	0.1770	0.1887
18	0.1785	0.1924
18.25	0.1797	0.1956
18.5	0.1808	0.1984
18.75	0.1816	0.2008
19	0.1823	0.2029
19.25	0.1829	0.2046
19.5	0.1833	0.2060
19.75	0.1837	0.2072
20	0.1839	0.2081
20.25	0.1841	0.2087
20.5	0.1842	0.2090
20.75	0.1842	0.2092
21	0.1841	0.2091
21.25	0.1840	0.2089
21.5	0.1838	0.2084
21.75	0.1835	0.2079
22	0.1832	0.2071
22.25	0.1828	0.2063
22.5	0.1823	0.2053
22.75	0.1818	0.2042
23	0.1812	0.2030
23.25	0.1806	0.2016
23.5	0.1799	0.2002
23.75	0.1792	0.1987
24	0.1785	0.1970
24.25	0.1777	0.1954
24.5	0.1769	0.1936
24.75	0.1761	0.1918
25	0.1753	0.1899
25.25	0.1745	0.1880
25.5	0.1737	0.1861
25.75	0.1729	0.1841
26	0.1721	0.1821
26.25	0.1713	0.1801
26.5	0.1705	0.1781

26.75	0.1697	0.1760
27	0.1690	0.1739
27.25	0.1682	0.1718
27.5	0.1674	0.1697
27.75	0.1666	0.1677
28	0.1658	0.1656
28.25	0.1650	0.1635
28.5	0.1642	0.1615
28.75	0.1634	0.1594
29	0.1625	0.1574
29.25	0.1617	0.1554
29.5	0.1608	0.1534
29.75	0.1599	0.1514
30	0.1590	0.1495
30.25	0.1581	0.1475
30.5	0.1572	0.1455
30.75	0.1562	0.1436
31	0.1553	0.1417
31.25	0.1543	0.1397
31.5	0.1533	0.1378
31.75	0.1523	0.1359
32	0.1512	0.1340
32.25	0.1501	0.1321
32.5	0.1490	0.1302
32.75	0.1479	0.1283
33	0.1467	0.1265
33.25	0.1456	0.1246
33.5	0.1444	0.1227
33.75	0.1431	0.1209
34	0.1418	0.1190
34.25	0.1406	0.1172
34.5	0.1392	0.1153
34.75	0.1379	0.1135
35	0.1365	0.1116
35.25	0.1351	0.1097
35.5	0.1337	0.1078
35.75	0.1322	0.1059
36	0.1308	0.1040
36.25	0.1292	0.1021
36.5	0.1277	0.1001

36.75	0.1262	0.0982
37	0.1246	0.0962
37.25	0.1230	0.0943
37.5	0.1214	0.0923
37.75	0.1197	0.0903
38	0.1180	0.0883
38.25	0.1164	0.0863
38.5	0.1147	0.0843
38.75	0.1129	0.0823
39	0.1112	0.0803
39.25	0.1094	0.0782
39.5	0.1076	0.0762
39.75	0.1058	0.0742
40	0.1040	0.0721
40.25	0.1022	0.0700
40.5	0.1003	0.0680
40.75	0.0985	0.0659
41	0.0966	0.0638
41.25	0.0947	0.0617
41.5	0.0928	0.0596
41.75	0.0909	0.0575
42	0.0889	0.0554
42.25	0.0870	0.0533
42.5	0.0850	0.0511
42.75	0.0830	0.0490
43	0.0811	0.0469
43.25	0.0791	0.0448
43.5	0.0771	0.0427
43.75	0.0751	0.0406
44	0.0731	0.0386
44.25	0.0710	0.0365
44.5	0.0690	0.0344
44.75	0.0670	0.0323
45	0.0650	0.0302
45.25	0.0630	0.0281
45.5	0.0609	0.0261
45.75	0.0589	0.0240
46	0.0568	0.0219
46.25	0.0548	0.0198
46.5	0.0527	0.0177

46.75	0.0507	0.0156
47	0.0486	0.0135
47.25	0.0465	0.0114
47.5	0.0445	0.0093
47.75	0.0424	0.0072
48	0.0403	0.0050
48.25	0.0382	0.0029
48.5	0.0361	0.0007
48.75	0.0339	-0.0015
49	0.0318	-0.0036
49.25	0.0297	-0.0058
49.5	0.0275	-0.0080
49.75	0.0254	-0.0103
50	0.0232	-0.0125
50.25	0.0210	-0.0147
50.5	0.0188	-0.0170
50.75	0.0166	-0.0193
51	0.0144	-0.0216
51.25	0.0122	-0.0239
51.5	0.0099	-0.0262
51.75	0.0077	-0.0285
52	0.0054	-0.0309
52.25	0.0032	-0.0332
52.5	0.0009	-0.0356
52.75	-0.0014	-0.0380
53	-0.0037	-0.0404
53.25	-0.0061	-0.0428
53.5	-0.0084	-0.0453
53.75	-0.0108	-0.0478
54	-0.0131	-0.0502
54.25	-0.0155	-0.0527
54.5	-0.0179	-0.0552
54.75	-0.0203	-0.0578
55	-0.0227	-0.0603
55.25	-0.0252	-0.0629
55.5	-0.0276	-0.0654
55.75	-0.0301	-0.0680
56	-0.0326	-0.0706
56.25	-0.0350	-0.0732
56.5	-0.0375	-0.0759

56.75	-0.0401	-0.0785
57	-0.0426	-0.0812
57.25	-0.0451	-0.0839
57.5	-0.0477	-0.0866
57.75	-0.0503	-0.0893
58	-0.0529	-0.0920
58.25	-0.0555	-0.0947
58.5	-0.0581	-0.0975
58.75	-0.0607	-0.1002
59	-0.0634	-0.1030
59.25	-0.0660	-0.1058
59.5	-0.0687	-0.1086
59.75	-0.0714	-0.1114
60	-0.0741	-0.1143
60.25	-0.0768	-0.1171
60.5	-0.0795	-0.1199
60.75	-0.0822	-0.1228
61	-0.0850	-0.1257
61.25	-0.0878	-0.1286
61.5	-0.0905	-0.1315
61.75	-0.0933	-0.1344
62	-0.0961	-0.1373
62.25	-0.0989	-0.1402
62.5	-0.1018	-0.1431
62.75	-0.1046	-0.1461
63	-0.1075	-0.1490
63.25	-0.1103	-0.1519
63.5	-0.1132	-0.1549
63.75	-0.1161	-0.1578
64	-0.1190	-0.1608
64.25	-0.1219	-0.1638
64.5	-0.1249	-0.1667
64.75	-0.1278	-0.1697
65	-0.1308	-0.1727
65.25	-0.1338	-0.1757
65.5	-0.1368	-0.1786
65.75	-0.1398	-0.1816
66	-0.1428	-0.1846
66.25	-0.1458	-0.1876
66.5	-0.1488	-0.1906

66.75	-0.1519	-0.1936
67	-0.1550	-0.1966
67.25	-0.1580	-0.1996
67.5	-0.1611	-0.2026
67.75	-0.1642	-0.2056
68	-0.1674	-0.2086
68.25	-0.1705	-0.2116
68.5	-0.1736	-0.2147
68.75	-0.1768	-0.2177
69	-0.1799	-0.2207
69.25	-0.1831	-0.2237
69.5	-0.1863	-0.2267
69.75	-0.1895	-0.2298
70	-0.1926	-0.2328
70.25	-0.1958	-0.2358
70.5	-0.1991	-0.2388
70.75	-0.2023	-0.2418
71	-0.2055	-0.2449
71.25	-0.2087	-0.2479
71.5	-0.2120	-0.2509
71.75	-0.2152	-0.2539
72	-0.2184	-0.2569
72.25	-0.2217	-0.2599
72.5	-0.2249	-0.2630
72.75	-0.2282	-0.2660
73	-0.2315	-0.2690
73.25	-0.2347	-0.2720
73.5	-0.2380	-0.2750
73.75	-0.2413	-0.2780
74	-0.2445	-0.2810
74.25	-0.2478	-0.2840
74.5	-0.2511	-0.2869
74.75	-0.2543	-0.2899
75	-0.2576	-0.2929
75.25	-0.2609	-0.2959
75.5	-0.2642	-0.2989
75.75	-0.2674	-0.3018
76	-0.2707	-0.3048
76.25	-0.2740	-0.3077
76.5	-0.2773	-0.3107

76.75	-0.2805	-0.3136
77	-0.2838	-0.3166
77.25	-0.2871	-0.3195
77.5	-0.2903	-0.3224
77.75	-0.2936	-0.3253
78	-0.2968	-0.3282
78.25	-0.3001	-0.3311
78.5	-0.3033	-0.3340
78.75	-0.3065	-0.3369
79	-0.3098	-0.3398
79.25	-0.3130	-0.3427
79.5	-0.3162	-0.3455
79.75	-0.3194	-0.3484
80	-0.3226	-0.3512
80.25	-0.3258	-0.3541
80.5	-0.3290	-0.3569
80.75	-0.3322	-0.3597
81	-0.3354	-0.3625
81.25	-0.3386	-0.3654
81.5	-0.3417	-0.3682
81.75	-0.3449	-0.3709
82	-0.3480	-0.3737
82.25	-0.3512	-0.3765
82.5	-0.3543	-0.3793
82.75	-0.3574	-0.3820
83	-0.3606	-0.3848
83.25	-0.3637	-0.3875
83.5	-0.3668	-0.3903
83.75	-0.3699	-0.3930
84	-0.3730	-0.3957
84.25	-0.3760	-0.3984
84.5	-0.3791	-0.4011
84.75	-0.3822	-0.4038
85	-0.3852	-0.4065
85.25	-0.3883	-0.4092
85.5	-0.3913	-0.4119
85.75	-0.3944	-0.4145
86	-0.3974	-0.4172
86.25	-0.4004	-0.4198
86.5	-0.4034	-0.4225

86.75	-0.4064	-0.4251
87	-0.4094	-0.4277
87.25	-0.4124	-0.4303
87.5	-0.4153	-0.4329
87.75	-0.4183	-0.4355
88	-0.4213	-0.4381
88.25	-0.4242	-0.4407
88.5	-0.4272	-0.4433
88.75	-0.4301	-0.4459
89	-0.4330	-0.4484
89.25	-0.4359	-0.4510
89.5	-0.4389	-0.4536
89.75	-0.4418	-0.4561
90	-0.4446	-0.4586
90.25	-0.4475	-0.4612
90.5	-0.4504	-0.4637
90.75	-0.4533	-0.4662
91	-0.4561	-0.4687
91.25	-0.4590	-0.4712
91.5	-0.4618	-0.4737
91.75	-0.4647	-0.4762
92	-0.4675	-0.4787
92.25	-0.4703	-0.4811
92.5	-0.4732	-0.4836
92.75	-0.4760	-0.4861
93	-0.4788	-0.4885
93.25	-0.4816	-0.4910
93.5	-0.4844	-0.4934
93.75	-0.4871	-0.4959
94	-0.4899	-0.4983
94.25	-0.4927	-0.5007
94.5	-0.4954	-0.5031
94.75	-0.4982	-0.5055
95	-0.5009	-0.5079