Statistical Analysis Plan

Sponsor Name: Armata Pharmaceuticals, Inc.

Protocol Number: AP-PA02-101

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

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

Approvals

Syneos Health Approval

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1. Glossary of Abbreviations

Abbreviation	Description
ADA	Anti-drug antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS/ERS	American Thoracic Society / European Respiratory Society
BMI	Body Mass index
bpm	beats per minute; breaths per minute
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CFR	Code of Federal Regulations
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFRSD	Cystic Fibrosis Respiratory Symptom Diary
CFTR	cystic fibrosis transmembrane conductance regulator
CFU	colony-forming units
CI	Confidence Interval
CRF	Case Report Form
CRISS	Chronic Respiratory Infection Symptom Score
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
dL	deciliter
DLT	Dose–Limiting Toxicity
ECG	Electrocardiogram
FDA	Food and Drug Administration
FEF_{25-75}	Forced Expiratory Flow between 25 and 75% of the FVC
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity

Abbreviation	Description
GCP	Good Clinical Practice
GLI	Global Lung Function Initiative
ICH	International Conference on Harmonization
INR	International Normalized Ratio
kg	kilogram
L	liter
LABA	long-acting inhaled β-agonist
LLQ	lower limit of quantification
LPS	lipopolysaccharide
MAD	Multiple Ascending Dose
Max	Maximum
µg	microgram
µL	microliter
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalent
mg	milligram
mL	milliliter
mmHg	millimeters of mercury
mmol	millimole
Min	Minimum
MOI	multiplicity of infection
N/A	Not Applicable
NA	Not Applicable
OR	Observational Research
PASS	Post Authorization Safety Study
PAES	Post Authorization Efficacy Study
Pa, P. aeruginosa	*Pseudomonas aeruginosa*
PFU	plaque-forming unit
PT	prothrombin time, preferred term
PTT	partial thromboplastin time
qs	quantity sufficient

Abbreviation	Description
QTc	corrected QT interval
QTcB	corrected QT interval using Bazett's formula
RR	respiratory rate
SABA	short-acting inhaled β-agonist
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	upper limit of normal
TEAE	Treatment Emergent Adverse Event
TFL	Table, Figure and Figure
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 that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

This SAP is created based on Protocol Number AP-PA02-101 version 6.0 dated 13 August 2021. The purpose of this SAP is to 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 is following 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 are responsible for the production and quality control of all SDTMs and ADaM datasets, and tables, figures and listings.

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 database through the time of the database lock. Analyses related to phage counts may be conducted by another entity, and as such are listed in this SAP for completeness, although no datasets and outputs are planned to be programmed by Syneos at this time,

No formal interim analyses for efficacy or futility are planned.

3. Study Objectives

3.1. Primary Objective

Part 1: SAD Evaluation: Evaluate the safety and tolerability of a single dose of AP-PA02 administered via inhalation.

Part 2: Multiple Ascending Dose (MAD) Evaluation: Evaluate the safety and tolerability of multiple doses of AP-PA02 administered via inhalation.

3.2. Secondary Objective(s)

Part 2: MAD Evaluation: To explore *P. aeruginosa* recovery in sputum following multiple doses of AP-PA02 administered via inhalation.

3.3. Exploratory Objectives

Part 1: SAD Evaluation: Examining phage distribution and clearance, evidence of clinical efficacy, and the impact of phage therapy on the bacterial target after a single dose of AP-PA02 administered via inhalation.

Part 2: MAD Evaluation: Examining phage distribution and clearance, evidence of clinical efficacy, and the impact of phage therapy on the bacterial target.

3.4. Brief Description

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

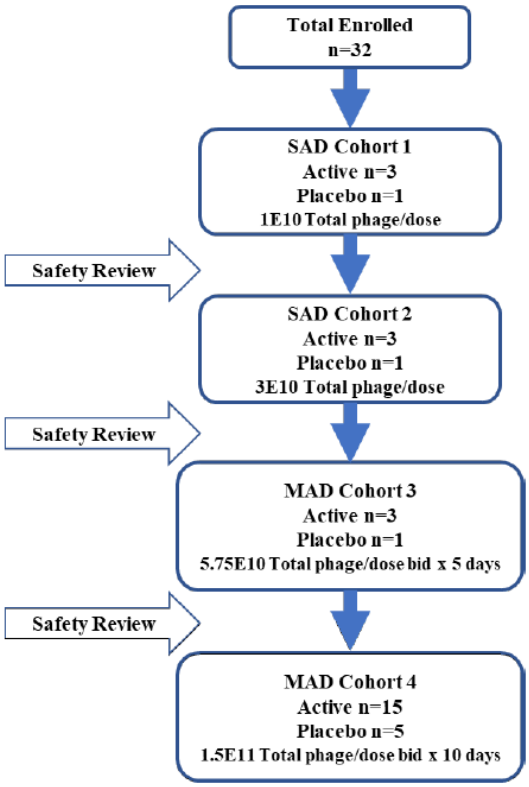
3.4.1. Part 1: SAD Evaluation

Part 1 will evaluate single ascending doses of AP-PA02 administered by inhalation in medically stable cystic fibrosis patients with pulmonary *P. aeruginosa* infection at time of Screening. A total of 8 subjects, 4 subjects in each of 2 sequential ascending dose cohorts, will be randomized to receive either AP-PA02 or placebo administered via inhalation at the clinical site. Each cohort of 4 subjects will be randomized with 3 subjects to receive active treatment and 1 subject to receive placebo.

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

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

Figure 3.1 Enrollment by Cohort Schematic



3.4.2. Part 2: MAD Evaluation

The MAD portion of the study will also be double-blinded, randomized, placebo-controlled, to evaluate the safety and efficacy of two dose levels of AP-PA02. The first MAD cohort (Cohort 3) will enroll 4 subjects, where 3 subjects will be randomized to active treatment and 1 subject randomized to receive placebo. The second MAD cohort (Cohort 4) will enroll 20 subjects, where 15 subjects will be randomized to receive active treatment, and 5 subjects will be randomized to receive placebo. The total number of placebo patients will be 6 subjects across the two dose cohorts.

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

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

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

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

3.5. Subject Selection

Subjects with cystic fibrosis and chronic pulmonary *Pa* infection 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 Section 6.1.1 and 6.1.2 of the protocol.

3.6. Determination of Sample Size

The sample size is not based on power calculations; it is chosen based on clinical experience and considered to be adequate to fulfill the objectives of the study.

Eight subjects were planned to be enrolled in the SAD portion of the study, with 4 subjects per cohort (3 AP-PA02 and 1 placebo).

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

3.7. Treatment Assignment & Blinding

This study has a single-dose phase and a multiple-dose phase and will include 4 separate cohorts based on Sections 3.4.1 and 3.4.2 (Figure 3.1).

The single-dose phase (Cohorts 1 and 2) will enroll subjects with medically stable cystic fibrosis with pulmonary *P. aeruginosa* infection at time of Screening prior to conducting a multiple-dose phase (Cohorts 3 and 4) in additional subjects.

The treatment allocation ratio for each SAD and MAD cohort will be 3:1, AP-PA02 to placebo. Due to the fact that there are four subjects per SAD cohort, at least one of the first two subjects enrolled in each cohort will be randomized to receive AP-PA02.

The first two subjects enrolled into the same SAD cohort will not be permitted to dose on the same day, to allow for adequate review of safety by the study Medical Monitor and/or Sponsor designee following dosing, as reported by the Investigator. If there are no significant findings for the first two subjects following their dosing, as reported by the Investigator(s), the remaining subjects of the cohort are permitted to undergo study drug dosing.

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

Study drug will be administered in a double-blind fashion. Study drug and placebo are both clear, colorless, and odorless aqueous solutions. Subjects, Investigators and study staff will be blinded to treatment assignment.

Rave RTSM will be used to assign subjects to treatment using a list of randomization codes generated by a randomizing statistician. No stratification factors will be used.

The subjects and all site personnel, including the investigator, the site monitor, and the study team, will be blinded with the exception of the following:

- RSG Project Lead
- Clinical Supply Manager
- Unblinded CRA
- Unblinded Lead CRA
- Unblinded Site Pharmacist
- Depot Users

Unblinding will occur after database lock and during review by the Safety Monitoring Committee (SMC).

3.8. Administration of Study Medication

Study drug doses will only be administered by a healthcare professional in an in-clinic setting. At-home dose administration will be allowed under supervision of a healthcare professional. Subjects will receive study drug by inhalation via the study-designated nebulizer.

Full details are available in the Investigational Medicinal Product and Nebulizer Sections 3.1 and 3.2 of the protocol.

3.9. Study Procedures

The study procedures to be performed as summarized in the Schedule of Assessments, is provided in the protocol Appendix 1, Schedule of Assessments.

4. Endpoints

4.1. Primary Endpoint

4.1.1. Part 1: SAD Evaluation

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

4.1.2. Part 2: MAD Evaluation

The primary endpoints of Part 2 of the trial are the incidence and severity of TEAEs, occurring from Day 1 pre-first dose through the EOS Visit.

4.2. Secondary Endpoints

4.2.1. Part 2: MAD Evaluation

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

4.3. Exploratory Endpoints

4.3.1. Part 1: SAD Evaluation

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

4.3.2. Part 2: MAD Evaluation

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

5. Analysis Sets

5.1. Safety/Efficay Population

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

5.2. Major 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.

6. General Aspects for Statistical Analysis

6.1. 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 SYNH programming standards and SAS validation procedures. Summaries will be presented by cohort/dose group and overall unless otherwise specified. Each active treatment group will be labeled in the outputs by its Phage Cocktail and estimated total protein per total plaque-forming units (PFU) for each dose for the SAD cohorts and the total dose per treatment course for the MAD cohorts. Additionally, pooled placebo will be presented.

The naming convention for the listings include:

- Cohort 1 Single Ascending Dose (SAD): 3-Phage Cocktail, AP-PA02 (1E10 PFU single dose)
- Cohort 1 Single Ascending Dose (SAD): 3-Phage Cocktail, Placebo
- Cohort 2 Single Ascending Dose (SAD): 3-Phage Cocktail, AP-PA02 (3E10 PFU single dose)
- Cohort 2 Single Ascending Dose (SAD): 3-Phage Cocktail, Placebo
- Am5 SAD: Single Ascending Dose (SAD): 3-Phage Cocktail, AP-PA02 (9E10 PFU single dose)
- Am5 SAD: Single Ascending Dose (SAD): 3-Phage Cocktail, Placebo
- Am5 MAD: Multiple Ascending Dose (MAD): 3-Phage Cocktail, AP-PA02 (1E10 PFU/dose x 3 doses/day x 3 days)
- Am5 MAD: Multiple Ascending Dose (MAD): 3-Phage Cocktail, Placebo
- Cohort 3 Multiple Ascending Dose (MAD): 5-Phage Cocktail, AP-PA02 (5.75E10 PFU/dose x 2 doses/day x 5 days)
- Cohort 3 Multiple Ascending Dose (MAD): 5-Phage Cocktail, Placebo
- Cohort 4 Multiple Ascending Dose (MAD): 5-Phage Cocktail, AP-PA02 (1.5E11 PFU/dose x 2 doses/day x 10 days)
- Cohort 4 Multiple Ascending Dose (MAD): 5-Phage Cocktail, Placebo
- “Screen Failures” if applicable

The naming convention for the tables and figures include:

- Cohort 1: 3-Phage (1E10 PFU SD)
- Cohort 2: 3-Phage (3E10 PFU SD)
- Cohort 3: 5-Phage (5.75E10 PFU/dose x 2 doses/day x 5 days)
- Cohort 4: 5-Phage (1.5E11 PFU/dose x 2 doses/day x 10 days)
- Pooled Placebo

Pooled Placebo group in the tables and figures will include Protocol Amendment 5 subjects.

Results for subjects assigned to either of the following dose groups will be included in the listings only:

- Am5 SAD: Single Ascending Dose (SAD): 3-Phage Cocktail, AP-PA02 (9E10 PFU single dose)
- Am5 MAD: Multiple Ascending Dose (MAD): 3-Phage Cocktail, AP-PA02 (1E10 PFU/dose x 3 doses/day x 3 days)

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.

A decision to close the study early was made by the Sponsor, and not all planned analysis outputs may be required.

6.2. Key Definitions

6.2.1. Baseline

Unless otherwise specified, baseline is defined as the last non-missing observation prior to the first dose of AP-PA02. Screening visit will be considered baseline if non-missing and the nominal visit 'Baseline' is missing. The Baseline Visit will be scheduled between Day -7 and Day -1 (inclusive) relative to Visit 1 Day 1 for all cohorts. Screening evaluations cannot be combined with evaluations performed as part of the Baseline Visit.

6.2.2. Study Day

The day of first dose of study drug 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 study drug administration, study days are numbered sequentially with negative values (i.e., Day -1, Day -2, etc.). There is no Day 0.

6.3. Missing Data

In general, missing data will not be imputed. All analyses will be based on observed cases. Sections 6.3.1 and 6.3.2 note the situations where missing data will be imputed.

6.3.1. 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 study drug 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.

6.3.2. 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 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.

6.4. 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, for example, 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 CTCAE laboratory grades.

6.5. Pooling of Centers

Data from all sites will be summarized together for analyses.

6.6. Subgroups

No subgroup analyses are planned for the study.

7. Demographic, Other Baseline Characteristics and Medication

7.1. 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.

7.2. Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by each cohort and overall for the Safety Population. The characteristics being summarized include: age at screening (in years), sex, 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 FEV_1 (L), FEV_1 % Predicted, FVC (L), FEF_{25-75} (L), sweat chloride (mEq/L), CFRSD-CRISS score, and CFQ-R Respiratory Symptoms Score.

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

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

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

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

7.3. 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 23.0 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.

7.4. Medication

Medications will be classified as prior (started prior and did not continue past the first dose of study treatment) and concomitant (continued past or started on or after the first dose date of study treatment).

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 2020.

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. 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.

7.4.1. Prior Medication

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

7.4.2. Concomitant Medication

Concomitant medications are defined as all medications taken during the study treatment period, including those which started before study treatment, but were reported ongoing at the first administration.

8. Efficacy

Observed values and changes from baseline for each efficacy endpoint in Sections 4.2 and 4.3 will be summarized with descriptive statistics at each scheduled time point based on the Safety Population for each dose cohort. Subjects will be analyzed as members of the treatment group to which they were randomized to.

8.1. Efficacy Endpoint and Analysis

Analysis of change in *P. aeruginosa* CFU per gram of sputum from Baseline through approximately 14 days after the last study drug dose of the MAD cohorts. Analysis of this exploratory endpoint will not be performed by Syneos Health.

8.2. Exploratory Efficacy Endpoint(s) and Analyses

8.2.1. Change in *P. aeruginosa* CFU per gram of sputum from Baseline through Visit 5 for SAD Cohorts

Analysis of this exploratory endpoint will not be performed by Syneos Health.

8.2.2. Change in *P. aeruginosa* isolates' sensitivity to AP-PA02 and/or its individual components

Analysis of this exploratory endpoint will not be performed by Syneos Health.

8.2.3. Change in *P. aeruginosa* isolates' sensitivity to antipseudomonal antibiotics

Analysis of this exploratory endpoint will not be performed by Syneos Health.

8.2.4. Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) from Day 1 pre-dose through end of study

Cystic Fibrosis Questionnaire-Revised (CFQ-R) subject health-related quality of life questionnaire assesses 12 domains: physical functioning, role functioning, vitality, emotional functioning, social functioning, body image, eating problems, treatment burden, health perceptions, weight, respiratory symptoms, and digestive symptoms.

Each domain is composed of a variable number of self-report questions with distinct 4-point Likert scales (e.g., always/often/ sometime/never), with a total of 50 questions. CFQ-R general scoring instructions are provided in Appendix 15.1. Each of the CFQ-R domains scores range from 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to the domain being evaluated. Domain scores are derived only when >50% of domain items are not missing.

The CFQ-R domain scaled score and absolute change from baseline will be summarized by visit using summary statistics for continuous variables by cohort and overall for each study part.

8.2.5. Changes in the Cystic Fibrosis Respiratory Symptom Diary (CFRSD) and Chronic Respiratory Infection Symptom Score (CRISS) from Day 1 pre-dose through the end of the study

The Cystic Fibrosis Respiratory Symptom Diary – Chronic Respiratory Infection Symptom Score (CFRSD-CRISS) is a subject-reported outcome that measures respiratory symptoms in cystic fibrosis using standard qualitative methods, includes 16 questions (8 symptom items, 4 emotional impact items, and 4 activity impact items) and takes less than 5 minutes to complete.

The eight respiratory symptom items will be rescored, summed, and converted to a 0 to 100 scale using the scoring guidelines of the Cystic Fibrosis Respiratory Symptom Diary (CFRSD) and Chronic Respiratory Infection Symptom Scale (CFRSD-CRISS), Version 2.0, 8 September 2016. The CFRSD-CRISS will not be calculated if more than one item response is missing. Scoring of the emotional and activity impact items is still under development and will not be summarized. The rescaling schema and conversion table are provided in Appendix 15.2. CFRSD severity score and absolute changes from baseline will be summarized for visits 2 through 6/EOS for SAD cohorts, and visits 2 through 8/EOS for MAD cohorts using summary statistics.

For SAD Visits 3, 4, 5, 6 and MAD Visits 6, 7, 8, 9 for Cohort 3 and MAD visits 11, 12, 13, and 14 for Cohort 4 under Protocol Version 6, there will be multiple days of diary data. The average daily score will be calculated for these multiple days and presented for a single visit corresponding to the Schedule of Assessments in Appendix 1 of the Protocol. Results for Daily Symptom Diary will be grouped to a single study visit if it occurs on the day of the study visit up until the day before the next visit is performed. For example, if a subject's Visit 3 occurs on Study Day 3, and Visit 4 occurs on Study Day 8, then the Daily Symptom Diary results for Study Day 3, 4, 5, 6, and 7 will be averaged and summarized for Visit 3.

9. 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), dose-limiting toxicities (DLTs), vital signs, laboratory assessments, immunogenicity, electrocardiogram (ECG) parameters, and physical examinations.

All safety information will be provided in subject listings.

9.1. Extent of Exposure

AP-PA-02 will be administered as a 3 mL loading volume for inhalation via the study nebulizer. Duration of treatment for SAD cohorts 1 and 2 will be one day and for the MAD cohorts 3 and 4 –two fractionated doses administered on five and ten consecutive days respectively (each of the two doses of a dose level is fractionated over two administrations).

Study drug 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 study drug inhalation, defined as last inhalation date – first inhalation date + 1. Total dose administration time for SAD cohorts is the elapsed time between start time and stop time of study drug 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 for MAD cohorts is defined similarly to SAD cohorts, for each dosing day, and for only the first dose of the day. Continuous variables will be summarized with descriptive statistics of mean, SD, median, minimum, and maximum.

9.2. Adverse Events

An overall summary of TEAEs will be provided, including the number and percentage of subjects who experience at least one of the following will be summarized by dose cohort and overall for each study part:

- 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 of interest
- DLTs
- 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 dose cohort and overall for each study part.

TEAEs are 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. This 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 23.0. 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 dose cohort and overall for each study part:

- 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
- 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
- TEAEs of Interest by SOC and PT
- DLTs by SOC and PT
- DLTs by severity, 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 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 severity or relationship to study drug, study device or study procedure, is missing for an AE, the event will be assumed to have severity level of 'severe' or the maximum relationship (i.e. definitely), respectively. If the seriousness status is missing for an AE, the event will be assumed to be serious.

9.2.1. Adverse Events of Interest

The AEs of interest include the following:

- Hypotension
- Acute Bronchospasm
- Hypoxia
- Tachycardia
- Acute Urticaria

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

In addition, a dose-limiting toxicity (DLT) is defined as follows, determined by the Investigator as study drug related:

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

9.3. Laboratory Evaluations

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

- Descriptive statistics of actual results and changes from baseline (number of subjects, mean, standard deviation, median, minimum, and maximum) for the continuous data and frequencies and percentages for the categorical data, for each assessment visit

- Potentially clinically significant lab abnormalities for hematology, chemistry and coagulation will be summarized by study part, dose group and assessment visit.

- By-subject line plots will be presented by lab parameter, study part and dose group, to allow for significant out of range values to be further identified

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 (hematology, serum chemistry, urinalysis, and coagulation).

Potentially clinically significant hematology and chemistry 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.

9.3.1. Hematology

Hematology will include a complete blood count (CBC), which includes hematocrit, hemoglobin, platelet count, and WBC (with absolute and/or relative differential of neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils).

9.3.2. Serum Chemistry

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

9.3.3. Urinalysis

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

9.3.4. Coagulation

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

9.4. Vital Signs

Vital sign measurements will consist of heart rate, respiratory rate, pulse, blood pressure (systolic and diastolic), temperature and oximetry. Descriptive summaries (number of subjects, mean, standard deviation, median, minimum, and maximum) of actual values and changes from pre-dose will be presented for each visit and time point, by study part and dose group. These summaries will be presented for the safety population and by dose cohort. Vital signs will be performed at prespecified time points per the Schedule of Assessments in Appendix 1 of the Protocol.

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

(Temperature (F) – 32) * 5/9 = Temperature (C)

Potentially clinically significant (PCS) vital sign abnormalities will be categorized based on Table 10.4.1, and summarized by study part, dose group and assessment visit.

Table 10.4.1: 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

Vital signs data will be listed chronologically by subject and visit for each vital sign parameter.

9.5. ECG

A 12-lead ECG will be performed locally at the site, and obtained at Screening, and pre-dose and 1 hour post dose on Day 1 for all subjects.

A shift table of the investigators' 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 dose group and overall. 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 participants 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 10.5.1: Potentially Clinically Significant Values for QT, QTcF, QTcB

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

9.6. Physical Examination

Complete physical examinations (urogenital exams not required) will be performed at Screening, Baseline and Visit 5 for subjects enrolled in the SAD cohorts. For MAD Cohorts, complete physical examinations will be performed at Screening, Baseline, and/or at the EOS Visit.

A by-subject listing will be provided, including body system and result by dose group and overall.

9.7. Spirometry

Spirometry assessments FEV_1, FVC, and FEF_{25-75} will be collected to evaluate for provoked bronchospasm. Actual liter values will be recorded. Details regarding spirometry procedures and standards will be included in the Study Manual.

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 dose 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, study part and dose group. Each dose group will be on a new plot, with all subjects of the same dose group on the same plot. Any unscheduled results will also be part of this plot.

The number and percentage of participants 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 10.7: 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

9.7.1. 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 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, otherwise = 0
coefficients a0… a6 depend on the measurement and gender
Mspline = age-varying coefficients

For 3-95 year-olds, Mspline is derived using linear interpolation with the assistance of a lookup table created by Qanjer, et. al. The lookup table contains values of known Mspline by age, and is used to calculate the unknown Mspline of the subjects age and sex. The coefficients used for predicted FEV_1 and a description of linear interpolation are provided in Appendix 15.3.

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

9.8. Pregnancy Test

Pregnancy test results will be provided in a listing.

9.9. Immunogenicity

Serum samples of AP-PA02 for ADA analyses for SAD, and MAD part of the study is described in Appendix 1 of the protocol. Immunogenicity sampling times and results will be listed for Safety population.

10. Interim Analyses

Safety will be assessed prior to each dose escalation by the SMC, as described in the protocol Section 9.1. No formal interim analyses for efficacy or futility are planned. Only personnel involved in phage titer analyses will be granted access to the unblinded data before database lock. No formal interim report will be generated.

11. Changes from Analysis Planned in Protocol

Not applicable.

12. Programming Considerations

All tables, listings, figures (TLFs), and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

12.1. General Considerations

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format or portable document format (pdf).
- Numbering of TLFs will follow ICH E3 guidance

12.2. Table, Listing, and Figure Format

12.2.1. General

- All TLFs will be produced in landscape format on A4/American letter size, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for all TLFs will have a minimum 1-inch blank margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used.
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

12.2.2. Headers

- All output should have the following header at the top left of each page:

  Armata Pharmaceuticals, Inc
  Protocol: AP-PA02-101

- All output should have the data cut-off date at the top right of each page.
- All output should have Page n of N at the top or bottom right corner of each page. TLFs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page. Each table should have the relevant listing number containing the raw data as a footer.

12.2.3. Display Titles

- Each TLF are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering convention will be followed. A decimal system (x.y and x.y.z) are used to identify TLFs with related contents. The title is centered. The analysis population is identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the
- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT population)

12.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the total column.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis population sizes will be presented for each column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis population.

12.2.5. Body of the Data Display

12.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

12.2.5.2. *Table Conventions*

- The summary tables will clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data.
- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean	XXX.X
SD	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. P-values less than 0.001 will be presented as <0.001. If a p-value is less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999.
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis population who have an observation will be the denominator. Percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of AE data are presented by the body system, treatment class, or SOC, PT, assuming all terms are coded. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as "-".

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed for the analysis population presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

12.2.5.3. *Listing Conventions*

- Listings will include days relative to the initiation of treatment as applicable.

- Listings will be sorted for presentation in order of subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available

12.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

12.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.

- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y.z’).

13. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health Standard Operating Procedure (SOP) Developing Statistical Programs (3907) .

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes 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."

14. Appendices

14.1. CFQ-R Scoring 3-4-2014 – General Scoring Instructions

For ease of interpretation, the questions on the CFQ-R are labeled according to the number on the questionnaire and the domain they are designed to measure. The domain label precedes the question number. For example the first question on the questionnaire is designed to measure a physical symptom and its label is “Phys1.” The complete labeling for each version of the CFQ-R is presented under the section entitled “Question Labels”.

The following scoring codes were written to be used with CFQ-R data that was entered into a database/spreadsheet where each question is a unique variable. The variable names should match the question labels listed in the “Question Labels” section. Values for each question range from 1 to 4. For questions with responses listed horizontally (left to right) the left response category should be assigned a value of 1, the second category should be assigned a 2, the third a 3, and the rightmost category should be assigned a 4.

Here is an example.

1. Performing vigorous activities such as running or playing sports……. **1** **2** **3** **4**

For questions that are listed vertically (top to bottom), the top category should be assigned a value of 1, the next a 2, the third a 3, and the bottom category a 4.

Here is an example.

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

It is important that you assign the values according to these rules for each question. Some of the questions will be phrased in a positive direction (like Question 13 listed above) and the values may seem inappropriate. The scoring codes reverse the ordering for these positively phrased questions. **Do not reverse the coding when you are entering the scores into your database/spreadsheet.** We have found it to be more accurate to let the scoring procedures address the reverse coding.

Please note that question 43 (resp43) on the Teen/Adult version and question 37 (resp37) on the Parent version have one extra category (don’t know) we typically assign a value of 5 to that category. This question is not included in the scoring of the respiratory scale.

N/A responses should be entered as missing (do not enter “0” for N/A, or the number zero will be counted as an actual response and will result in an inaccurate domain score)

14.1.1. Question Labels - CFQ-R Teen/Adult Version

Question 1 = phys1
Question 2 = phys2
Question 3 = phys3
Question 4 = phys4
Question 5 = phys5
Question 6 = vital6
Question 7 = emot7
Question 8 = emot8
Question 9 = vital9
Question 10 = vital10
Question 11 = vital11
Question 12 = emot12
Question 13 = phys13
Question 14 = eat14
Question 15 = treat15
Question 16 = treat16
Question 17 = treat17
Question 18 = health18
Question 19 = phys19
Question 20 = phys20
Question 21 = eat21
Question 22 = social22
Question 23 = social23
Question 24 = body24
Question 25 = body25
Question 26 = body26
Question 27 = social27
Question 28 = social28
Question 29 = social29
Question 30 = social30
Question 31 = emot31
Question 32 = health32
Question 33 = emot33
Question 34 = health34
Question 35 = role35
Question 36 = role36
Question 37 = role37
Question 38 = role38
Question 39 = weight39
Question 40 = resp40
Question 41 = resp41
Question 42 = resp42
Question 43 = resp43
Question 44 = resp44
Question 45 = resp45

Question 46 = resp46
Question 47 = digest47
Question 48 = digest48
Question 49 = digest49
Question 50 = eat50

14.1.2. SAS Program Codes for Scoring the CFQ-R Teen/Adult Version

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

Data CFQR_TA; set CFQR_TA;

/* Recoding Some Variables */

vital6      =   5-vital6;
vital10     =   5-vital10;
phys13      =   5-phys13;
treat15     =   5-treat15;
treat17     =   5-treat17;
health18    =   5-health18;
social23    =   5-social23;
social28    =   5-social28;
social30    =   5-social30;
health32    =   5-health32;
health34    =   5-health34;
role35      =   5-role35;
resp43      =   5-resp43;

/* Calculating Scores */

if nmiss (phys1, phys2, phys3, phys4, phys5, phys13, phys19, phys20) <= 4 then
physical = (mean (phys1, phys2, phys3, phys4, phys5, phys13, phys19, phys20)-1)/3*100;

if nmiss (role35, role36, role37, role38) <= 2 then
role = (mean (role35, role36, role37, role38)-1)/3*100;

if nmiss (vital6, vital9, vital10, vital11) <= 2 then
vitality = (mean (vital6, vital9, vital10, vital11)-1)/3*100;

if nmiss (emot7, emot8, emot12, emot31, emot33) <= 2 then
emotion = (mean (emot7, emot8, emot12, emot31, emot33)-1)/3*100;

if nmiss (social22, social23, social27, social28, social29, social30) <= 3 then
social = (mean (social22, social23, social27, social28, social29, social30)-1)/3*100;
```

```
if nmiss (body24, body25, body26) <= 1 then
body = (mean (body24, body25, body26)-1)/3*100;

if nmiss (eat14, eat21, eat50) <= 1 then
eat = (mean (eat14, eat21, eat50)-1)/3*100;

if nmiss (treat15, treat16, treat17) <= 1 then
treat = (mean (treat15, treat16, treat17)-1)/3*100;

if nmiss (health18, health32, health34) <= 1 then
health = (mean (health18, health32, health34)-1)/3*100;

if nmiss (weight39) = 0 then
weight= (mean (weight39)-1)/3*100;

if nmiss (resp40, resp41, resp42, resp44, resp45, resp46) <= 3 then
respirat = (mean (resp40, resp41, resp42, resp44, resp45, resp46)-1)/3*100;

if nmiss (digest47, digest48, digest49) <= 1 then
digest = (mean (digest47, digest48, digest49)-1)/3*100;
run;
```

14.2. Cystic Fibrosis Respiratory Symptom Diary (CFRSD) and Chronic Respiratory Infection Symptom Scale (CFRSD-CRISS), Scoring Guidelines

The Rasch-derived CFRSD-CRISS is computed by rescoring the eight respiratory symptom items, summing the rescored items, and converting to a 0 to 100 scale. The CFRSD-CRISS should not be calculated if more than one item response is missing. Scoring of the emotional and activity impact items is still under development. The rescaling schema and conversion table are provided below. Rescore item responses as follows:

Q1. During the last 24 hours… How difficult was it to breathe?

Response	Raw Score	Item Score
Not difficult	1	0
A little difficult	2	1
Somewhat difficult	3	1
A good deal difficult	4	2
A great deal difficult	5	3

Q2. During the last 24 hours… How feverish did you feel (have a temperature)?

Response	Raw Score	Item Score
Not feverish	1	0
A little feverish	2	1
Somewhat feverish	3	1
A good deal feverish	4	1
A great deal feverish	5	2

Q3. During the last 24 hours… How tired did you feel?

Response	Raw Score	Item Score
Not tired	1	0
A little tired	2	1
Somewhat tired	3	1
A good deal tired	4	2
A great deal tired	5	3

Q4. During the last 24 hours… How bad were your chills or sweats?

Response	Raw Score	Item Score
No chills or sweats	1	0
Slightly Bad	2	1
Moderately Bad	3	1
Very Bad	4	2
Extremely Bad	5	3

Q5. During the last 24 hours… How bad was your cough?

Response	Raw Score	Item Score
No cough	1	0
Slightly Bad	2	1
Moderately Bad	3	2
Very Bad	4	3
Extremely Bad	5	4

Q6. During the last 24 hours… How much mucus did you cough up?

Response	Raw Score	Item Score
No mucus	1	0
A little mucus	2	1
Some mucus	3	2
A good deal of mucus	4	3
A great deal of mucus	5	4

Q7. During the last 24 hours… How much tightness in the chest did you have?

Response	Raw Score	Item Score
No tightness	1	0
A little tightness	2	1
Some tightness	3	1
A good deal of tightness	4	2
A great deal of tightness	5	3

Q8. During the last 24 hours… How bad was your wheezing?

Response	Raw Score	Item Score
No wheezing	1	0
Slightly Bad	2	1
Moderately Bad	3	1
Very Bad	4	1
Extremely Bad	5	2

Raw Summed Score= Sum of Q1 through Q8 Item Scores (range 0-24).
Convert Summed Score to CFRSD Severity Score using the table below.

Summed Score to CFRSD Severity Score Conversion Table

Summed Score	CFRSD Severity Score	Summed Score	CFRSD Severity Score
0	0	13	59
1	14	14	61
2	23	15	63
3	29	16	65
4	34	17	68
5	37	18	70
6	41	19	73
7	44	20	76
8	46	21	80
9	49	22	85
10	52	23	91
11	54	24	100
12	56		

14.3. GLI Regression Coefficients and Linear Interpolation

The linear coefficients used in conjunction with the lookup tables for calculating the Mspline value 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

Linear interpolation is a form of curve fitting and has the following form:

$$y = y_0 + (x - x_0)\frac{y_1 - y_0}{x_1 - x_0}$$

Applied to the GLI 2012 regression equations, the variables will be defined as the following:
x = age of subject
y= the unknown Mspline value at age x
y0 = the known Mspline value for age x0, using lookup tables
y1 = the known Mspline value for age x1, using lookup tables
x0 = age value lower bound
x1 = age value upper bound

For example, for a male aged 12.2 years, the lookup table has the following known Mspline values for 12 years, the lower bound, and 12.25, the upper bound:

age	Mspline
12	-0.0176
12.25	-0.0101

Therefore, Mspline = -0.0176 + (12.2-12)*(-0.0101- (-0.0176))/(12.25 - 12) = -0.0116

15. Reference List

Implementing GLI 2012 lung function regression equations. GLOBAL LUNGS INITIATIVE. ERS Task Force (TF-2009-03) to establish improved Lung Function Reference Values Chairs: J Stocks, X. Baur, G. Hall, B. Culver.

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