



Statistical Analysis Plan

Investigational Product:	ARO-MUC5AC Inhalation Solution
Protocol Title:	A Phase 1/2A Study Evaluating the Effects Of ARO-MUC5AC Inhalation Solution In Healthy Subjects And Patients With Muco-obstructive Lung Disease
Study Number:	AROMUC5AC-1001
Sponsor:	Arrowhead Pharmaceuticals, Inc. 177 East Colorado Boulevard, Suite 700 Pasadena, CA 91105 USA
Author:	[REDACTED] [REDACTED] [REDACTED]
Protocol Version:	Original
SAP Version:	1.0
SAP Approval Date:	24Feb2025

Signature Page

Protocol Title:	A Phase 1/2A Study Evaluating The Effects Of ARO-MUC5AC Inhalation Solution In Healthy Subjects And Patients With Muco-obstructive Lung Disease
Protocol Number:	Protocol Amendment 4.0 Dated 21Feb2024
SAP Version/Date:	Final v1.0 / 25Feb2025

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature

Date

[Redacted Signature]

[Redacted Signature]

Arrowhead Pharmaceuticals, Inc.

[Redacted Signature]

[Redacted Signature]

Arrowhead Pharmaceuticals, Inc.

[Redacted Signature]

[Redacted Signature]

Arrowhead Pharmaceuticals, Inc.

[Redacted Date]

Version Number	Date (DDMMYYYY)	Summary of Changes
Original (v1.0)	24FEB2025	N/A

Table of Contents

1. INTRODUCTION	8
2. STUDY OVERVIEW	8
2.1. Objectives	8
2.1.1. Primary Objective	8
2.1.2. Secondary Objectives.....	8
2.1.3. Exploratory Objectives	8
2.2. Study Design.....	8
2.2.1. Overview.....	8
2.2.2. Randomization and Blinding	10
2.3. Study Endpoints	10
2.3.1. Primary Endpoints	10
2.3.2. Secondary Endpoints	11
2.3.3. Exploratory Endpoints	11
3. Statistical Methodology	12
3.1. General Considerations.....	12
3.1.1. Summary Statistics.....	12
3.1.2. Baseline and Study Day	12
3.1.3. Analysis Visit Window	13
3.1.4. Missing Data	13
3.2. Analysis Population	14
3.2.1. Safety Analysis Set	14
3.2.2. PK Analysis Set	14
3.3. Subject Data and Study Conduct	14
3.3.1. Subject Disposition	14
3.3.2. Protocol Deviations.....	14
3.3.3. Demographics and Baseline Characteristics	14
3.3.4. Medical History	15
3.3.5. Concomitant Medications and Procedures.....	15
3.3.6. Exposure	15
3.4. Safety Analyses.....	15
3.4.1. Adverse Events	16
3.4.2. Laboratory Tests Results.....	16

3.4.3.	Vital Signs.....	17
3.4.4.	12-Lead Electrocardiograms (ECG)	17
3.4.5.	Physical Examinations	17
3.4.6.	Chest X-rays.....	18
3.5.	Pharmacodynamic (PD) Analysis	18
3.5.1.	Mucin Measurements.....	18
3.5.2.	Fractional Exhaled Nitric Oxide (FeNO).....	18
3.5.3.	Blood Eosinophil or Neutrophil Count, Serum Total IgE, Plasma Periostin.....	18
3.6.	Efficacy Analysis	18
3.6.1.	Spirometry.....	18
3.6.2.	Mucus Symptom Assessments.....	19
3.6.3.	COPD Assessment Test	19
3.6.4.	SGRQ-C.....	19
3.7.	Pharmacokinetic (PK) Analysis.....	19
3.7.1.	Pharmacokinetic Profile Exclusions	20
3.7.2.	Below the Limit of Quantification.....	20
3.7.3.	Missing Data	20
3.7.4.	Predose Samples Collected Postdose.....	20
3.7.5.	Summary Statistics.....	20
3.7.6.	PK Concentrations	21
3.7.7.	PK Parameters.....	21
4.	Change From Protocol-Specified Statistical Analyses	22
5.	PROGRAMMING SPECIFICATIONS	22

List of abbreviations and definitions of terms

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BALF	bronchoalveolar lavage fluid
BLQ	below the limit of quantification
BMI	body mass index
CAT	COPD assessment test
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CSR	clinical study report
CTCAE	national cancer Institute common terminology criteria for adverse events
CV	coefficient of variation
DSC	data safety committee
ECG	electrocardiogram
EOS	end of study
FEF ₂₅₋₇₅	forced mid-expiratory flow
FeNO	fractional exhaled nitric oxide
FEV ₁	forced expiratory volume
FIH	first in human
FSH	follicle-stimulating hormone
FVC	forced vital capacity
HR	heart rate
ICF	informed consent form
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IL	interleukin
IP	investigational product
IRB	Institutional Review Board
IWRS	interactive web response system
LLN	lower limit of normal

Abbreviation	Definition
MAD	multiple ascending dose
MedDRA	medical dictionary for regulatory activities
mRNA	messenger RNA
MUC5AC	mucin 5AC
MUC5B	mucin 5B
NHV	normal healthy volunteer
PD	pharmacodynamics
PI	principal investigator
PK	pharmacokinetics
ppFEV ₁	percent predicted FEV ₁
PR	PR interval
PT	preferred term
QA	quality assurance
QRS	QRS complex
QT	QT interval
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
RR	RR interval
SAD	single ascending dose
SAE	serious adverse event
SD	standard deviation
SGRQ-C	St. George's Respiratory Questionnaire for COPD Patients
SI	international system
SOC	System Organ Class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO-DD	world health organization drug dictionary

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined in the protocol version 4.0 for study AROMUC5AC-1001 dated 21 Feb 2024. The scope of this plan includes the planned final analyses to be included in the Clinical Study Report (CSR).

2. STUDY OVERVIEW

2.1. Objectives

2.1.1. Primary Objective

- To assess the safety and tolerability of ARO-MUC5AC in normal healthy volunteer (NHVs) and patients

2.1.2. Secondary Objectives

- To assess the pulmonary safety of ARO-MUC5AC in NHVs and patients using spirometry
- To assess the pharmacokinetics (PK) of ARO-MUC5AC in NHVs and patients

2.1.3. Exploratory Objectives

- To assess the pharmacodynamics (PD) of ARO-MUC5AC in NHVs and patients
- To assess the efficacy of ARO-MUC5AC in patients

2.2. Study Design

2.2.1. Overview

This is a Phase 1/2a, randomized, double-blind, placebo-controlled first in human (FIH) study of ARO-MUC5AC in NHVs and patients with moderate-to-severe asthma and patients with moderate-to-severe COPD. The purpose of this study is to evaluate the safety, tolerability, PK, PD, and efficacy of ARO-MUC5AC. The study is divided into initial NHV cohorts evaluating single ascending doses (SADs), followed by NHV and patient cohorts evaluating multiple ascending doses (MADs).

ARO-MUC5AC is intended for use in patients with airways disease; however, because these patients may have baseline decreased lung function and are frequently on multiple concomitant medications, this study first evaluates dose levels in an NHV population to generate a baseline understanding of safety in a population with normal airway physiology and limited concomitant medication use prior to evaluating dose levels in patients. Additionally, NHV cohorts will generate an initial understanding of dose response using sputum MUC5AC concentration as a biomarker of PD effect.

For all cohorts, participants who have signed an Independent Ethics Committee (IEC) /Institutional Review Board (IRB)-approved informed consent form (ICF) and met all the

protocol eligibility criteria during Screening will be randomized to receive ARO-MUC5AC or placebo.

The SAD portion of the study includes 4 sequentially enrolled NHV cohorts treated with escalating single-dose levels. For each subject, a single dose at a fixed dose level will be administered once on Day 1 and the subject will be monitored up to Day 29. All subjects within a cohort will receive the same dose. Each cohort will contain 6 subjects (4 active:2 placebo). Each single-dose cohort will begin with administration of ARO-MUC5AC or placebo to 2 sentinel participants (1 ARO-MUC5AC, 1 placebo). Following the Day 2 evaluation in the sentinel participants, if there are no significant safety concerns based on the Principal Investigator's (PI's) judgment, the remaining participants in the cohort will be dosed. The dosing of participants in single-dose cohorts will be staggered by at least 30 minutes such that no 2 participants will be dosed simultaneously.

Based on available observations for all NHV subjects in each of the single-dose cohorts through the Day 15 visit, and experience from other prior cohorts (ie, all cumulative available safety data), the Data Safety Committee (DSC) will meet to vote on the following (see Study Schema, [Figure 1](#)):

- Dose escalation to the next single-dose NHV cohort
- Initiation of multiple-dose NHV and patient cohorts when applicable per the Study Schema ([Figure 1](#))

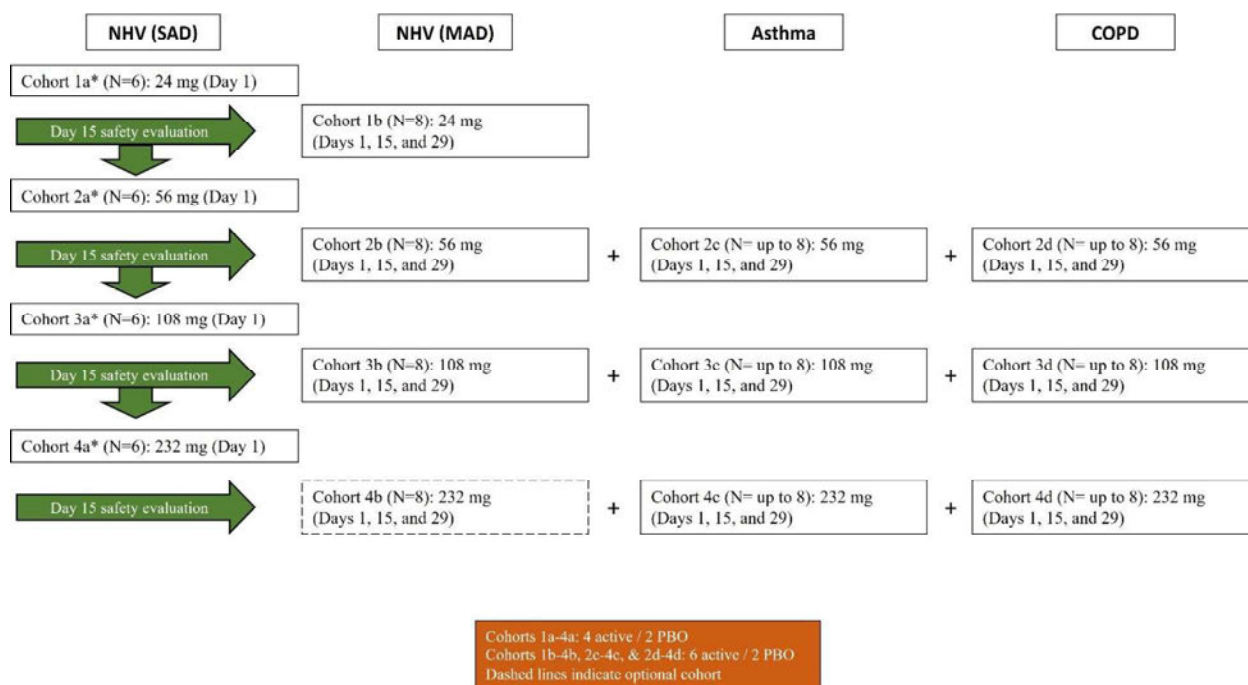
The MAD portion of the study consists of the following cohorts: 4 NHV, 3 asthma patient, and 3 COPD patient. For both the NHV and patient cohorts, each sequential cohort will be treated with an escalating dose level. For each subject, 3 total doses at a fixed dose level will be administered, with 1 dose given on each of Days 1, 15, and 29, and the subject will be monitored up to Day 85. All subjects within a cohort will receive the same dose. Each MAD cohort will contain 8 subjects (6 active:2 placebo). No sentinel dosing will be performed in multiple-dose cohorts as all dose levels will have already been tested in single-dose cohorts. NHV MAD Cohort 4b is optional and may be enrolled at the discretion of the Sponsor following DSC approval of cohort opening.

Screening for the multiple-dose cohorts can begin prior to DSC approval of cohort opening, but dose administration may not proceed until after the DSC has opened the designated multiple-dose cohort. Multiple-dose NHV and patient cohorts will be opened for accrual once the NHV single-dose cohort at the corresponding dose level has reached Day 15 and based on a DSC vote that it is safe to proceed. Multiple-dose NHV cohorts will enroll sequentially from Cohort 1b through Cohort 4b. Multiple-dose patient cohorts may enroll in parallel with multiple-dose NHV cohorts receiving the same dose level (eg, asthma Cohort 2c may enroll in parallel with NHV Cohort 2b, see Study Schema).

Escalation to the next highest dose level will proceed until the highest planned dose level is completed or the trial is halted prematurely by the PI, DSC, or Sponsor due to safety or other concerns.

For all cohorts, the indicated dose level is the maximum allowable dose for the cohort, but the Sponsor may adjust the dose downward based on available safety and PD data.

Figure 1: Study Schema



Abbreviations: COPD=chronic obstructive pulmonary disease; MAD=multiple ascending dose; NHV=normal healthy volunteer; PBO=placebo; SAD=single ascending dose.

Note: Cohorts 1a to 4a (*) each use 2 sentinel subjects dosed before rest of the cohort. Dose levels indicate the dose loaded into the nebulizer (nebulizer-loaded dose).

2.2.2. Randomization and Blinding

Eligible subjects will be allocated a unique randomization number, in accordance with the randomization schedule, to one of two possible treatment groups: ARO-MUC5AC or Placebo. Treatments will be administered per the randomized sequence generated by interactive web response system (IWRS). The randomization numbers will be grouped in blocks. Each cohort of NHV (SAD) subjects will contain two blocks, the first will contain two subjects as a sentinel pair randomized to: 1 ARO-MUC5AC and 1 Placebo, and the remaining blocks will contain the remaining four subjects randomized to: 3 ARO-MUC5AC and 1 Placebo. Each cohort of NHV (MAD), Asthma and COPD subjects will contain one block consisting of eight subjects randomized to: 6 ARO-MUC5AC and 2 Placebo.

Investigators and study participants will remain blinded to treatment allocation of subjects through end of study (EOS). Selected Sponsor members will be unblinded to treatment allocation of subjects throughout the entire study. This study will be unblinded to study team after database lock.

2.3. Study Endpoints

2.3.1. Primary Endpoints

- The incidence and frequency of treatment-emergent adverse events (TEAEs) over time through EOS

2.3.2. Secondary Endpoints

- Change from baseline over time through EOS in forced expiratory volume (FEV₁) as a safety assessment
- Change from baseline over time through EOS in forced vital capacity (FVC) as a safety assessment
- Plasma PK parameters of ARO-MUC5AC

2.3.3. Exploratory Endpoints

Safety:

- Change from baseline to Day 38 in bronchoalveolar lavage fluid (BALF) cell count and differential in NHVs
- Change from baseline over time through EOS in chest x-ray findings
- Incidence and titer of anti-drug antibodies over time through EOS

Pharmacokinetics/Pharmacodynamics:

- Change from baseline over time through EOS in mucin 5AC (MUC5AC) and mucin 5B (MUC5B) protein concentrations from induced sputum samples
- Change from baseline to Day 38 in MUC5AC and MUC5B protein concentrations in bronchoscopic airway swab samples and bronchosorption samples from NHVs
- Change from baseline to Day 38 in MUC5AC and MUC5B protein concentrations in BALF samples from NHVs
- Change from baseline over time through EOS in MUC5AC and MUC5B messenger RNA (mRNA) expression from induced sputum samples
- Change from baseline to Day 38 in MUC5AC and MUC5B mRNA expression from BALF samples
- Change from baseline over time through EOS in serum total immunoglobulin E (IgE) concentrations in patients
- Change from baseline over time through EOS in plasma periostin in patients
- Change from baseline over time through EOS in fractional exhaled nitric oxide (FeNO) in patients
- Change from baseline over time through EOS in blood eosinophil or neutrophil count in patients
- Identification of ARO-MUC5AC metabolites in plasma and urine after a single dose of study drug in NHVs

Efficacy:

- Change from baseline over time through EOS in mucus symptom assessment in patients

- Change from baseline over time through EOS in prebronchodilator and postbronchodilator FEV₁ in patients
- Change from baseline over time through EOS in prebronchodilator and postbronchodilator forced mid-expiratory flow (FEF₂₅₋₇₅) in patients
- Change from baseline over time through EOS in CAT score in patients
- Change from baseline over time through EOS in the St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C) in patients

3. STATISTICAL METHODOLOGY

3.1. General Considerations

3.1.1. Summary Statistics

No formal statistical tests of hypotheses will be performed. In general, continuous data will be summarized by descriptive statistics, including number of subjects, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the number and percentage of subjects. Data will be analyzed by population (NHV subjects, patients with asthma, and patients with COPD) and treatment groups. For each population, subjects who receive placebo will be pooled.

3.1.2. Baseline and Study Day

Day 1

Day 1 is defined as the date of first administration of study drug. If the date of first study drug administration is missing, date of randomization will be used as Day 1. Study day is calculated relative to the date of Day 1 as follows:

- For any events on or after the first administration of the study drug, study day is calculated as: event date – date of first administration of study drug + 1.
- For any events before the first administration date, study day is calculated as: event date – date of first administration of study drug. As such, one day before the first administration date is study day -1.

Baseline

Generally, baseline is defined as the predose value occurring closest to the first investigational product (IP) administration.

For MUC5AC and MUC5B, baseline is defined as average of all predose values.

End of Study Date

The EOS Date is defined as the date that the planned EOS or Early Termination visit occur. E.g. NHV Cohorts (Cohorts 1a-4a) EOS is recorded Day 29/Early Termination date. Multiple-Dose NHV Cohorts (Cohorts 1b-4b) EOS is recorded Day 85/Early Termination Date. Multiple-Dose

Asthmatic Cohorts (Cohorts 2c – Cohorts 4c) and Multiple-Dose COPD Cohorts (Cohorts 2d – Cohorts 4d) EOS is recorded Day 85/Early Termination Date.

3.1.3. Analysis Visit Window

No analysis visit window will be defined for this study. All endpoints will be analyzed according to the nominal visits (i.e. assigned visit).

3.1.4. Missing Data

Subjects may be missing specific data points for various reasons. Queries will be made to the sites to distinguish true missing values from other unknown values (e.g. due to measurement of sample processing error). All attempts will be made to capture missing or partial data for the study prior to database lock.

Missing values will not be imputed except for missing or partial dates of AEs, concomitant status for medication and procedures, and for missing or partial dates where a complete date is required for calculations. When relevant, sections below will address how missing data will be handled for the particular analyses.

Adverse Events (AEs):

- AEs that cannot be definitely determined as occurring prior to study drug administration will be counted as TEAEs unless either the partial start date/time or a partial or complete end date/time documents the AE as occurring prior to treatment.
- TEAE start date:
 - TEAE imputed dates will not be earlier than the subject's Day 1 date.
 - If all year, month, and day are missing then use the subject's Day 1 date.
 - If year is available but day and month are missing, the day and month for the start date will be set to the 1st of January of the onset year.
 - If year and month are available but day is missing, the day will be set to the 1st of the month of the onset year.
- End date will not be imputed

Concomitant medications (CMs):

- Medications with missing or partial end dates will be assumed to be concomitant unless a partial end date documents it as ending prior to treatment.
- CM start date:
 - If all year, month, and day are missing then use the subject's Day 1 date.
 - If year is available but day and month are missing, the day and month for the start date will be set to the 1st of January of the onset year.
 - If year and month are available but day is missing, the day will be set to the 1st of the month of the onset year.
- End date will not be imputed

3.2. Analysis Population

3.2.1. Safety Analysis Set

All subjects who receive at least 1 dose of IP. All analyses except for PK analysis will be performed using this set. Subjects will be analyzed according to the received treatment.

3.2.2. PK Analysis Set

All subjects who receive at least 1 dose of IP and have at least one quantifiable post-dose PK concentration. Subjects with major protocol violations will be assessed on a subject-by-subject basis for inclusion in PK Analysis Set. The PK Analysis Set will be used for PK analyses.

3.3. Subject Data and Study Conduct

3.3.1. Subject Disposition

Subject disposition will be summarized as the number and percentage of subjects who were randomized, received the treatment, complete the treatment, complete the study, discontinued treatment, discontinued study by treatment group for all randomized subjects. Disposition will be listed by treatment and subject.

3.3.2. Protocol Deviations

Protocol deviation listing will be presented by subject.

3.3.3. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment and in total based on the Safety Analysis Set.

The following demographic and baseline characteristics will be summarized:

- Age (years)
- Sex at Birth
- Childbearing potential and non-childbearing status
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)

For patients with asthma, the following baseline disease characteristics will be summarized:

- Age of patient at asthma onset (years)
- Presence of Atopy

- Number of total asthma exacerbations in the previous year
- Number of total asthma exacerbations in the previous year that resulted in hospitalization
- History of FEV₁ reversibility

For patients with COPD, the following baseline disease characteristics will be summarized:

- Age at diagnosis of COPD (years)
- Number of total COPD exacerbations in the previous year
- Number of moderate or severe COPD exacerbations in the previous year
- Smoking history

Subject data listings containing baseline disease characteristics will be provided.

3.3.4. Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or higher. Counts and percentages of subjects with medical history by system organ class and preferred term will be summarized by treatment and in total based on the Safety Analysis Set.

A subject data listing containing medical history will be provided.

3.3.5. Concomitant Medications and Procedures

Prior medications are defined as medications with start time prior to the time of study drug administration, regardless of when the medication stops.

Concomitant medications are defined as medications which is taken any time after the first dose of study drug, regardless of when the medication starts or stops.

The number and percentage of subjects with concomitant medications will be summarized by World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classification and preferred term (PT) by treatment group in the Safety Analysis Set.

The data will be listed by subject.

3.3.6. Exposure

Study drug administration data will be listed by subject. The number of doses receiving for each subject will be summarized with counts and percentages by treatment group in the Safety Analysis Set.

3.4. Safety Analyses

Safety analyses will be performed based on Safety Analysis Sets. Results will be summarized by treatment and cohort. Placebo subjects from each healthy volunteer cohort will be pooled.

3.4.1. Adverse Events

AE terms will be coded using the MedDRA dictionary version 24.1 or higher. A TEAE is defined as an AE that occurs following IP administration or a pre-existing condition exacerbated following IP administration.

The severity of all AEs will be graded using the latest version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

An overall AE summary will be presented by the number and percent of subjects with the following:

- All TEAEs
- Serious TEAEs
- Study drug-related TEAEs
- Study drug-related serious TEAEs
- TEAEs by maximum severity grade
- TEAEs leading to study drug discontinuation
- TEAEs leading to study discontinuation
- TEAEs leading to death

The incidence and frequency of AEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT) in decreasing order of frequency for the following categories:

- TEAEs
- TEAEs by maximum severity grade
- Serious TEAEs
- Related TEAEs
- Related serious adverse event (SAEs)
- TEAEs leading to study discontinuation, drug interruption, or drug withdrawal

Additionally, the incidence and frequency of TEAEs will be summarized by PT in decreasing order of frequency.

At each level of summarization, a subject will be counted once if he/she reported one or more events. The severity grade and relationship to study drug will be summarized in a similar manner.

3.4.2. Laboratory Tests Results

Clinical laboratory values will be expressed using International System of Units (SI) units.

The actual value and derived change from Baseline to each protocol-specified scheduled visit/time point will be summarized for each clinical laboratory test from the clinical lab assessments: hematology, blood chemistry, coagulation, and urinalysis.

The incidence of lab abnormalities will be summarized by visit/time point for clinical lab tests from hematology and blood chemistry lab assessments. Results will be classified as “Low” when below the lower limit of normal ($< LLN$), “High” when above the upper limit of normal ($> ULN$), and “Normal” when within the normal limits (Normal), as applicable. Unscheduled assessments will be included in abnormality summary tables.

Subject data listings will be provided for the following assessments. As applicable, listings will include abnormality classifications: “Low” when classified as below the lower limit of normal, “High” when above the upper limit of normal, and “Normal” when within the normal limits.

- Hematology data
- Blood chemistry data
- Coagulation data
- Urinalysis data
- COVID-19 testing data
- Drug screen data
- Urine Cotinine data
- Pregnancy, including follicle-stimulating hormone (FSH), data
- Other clinical laboratory data

3.4.3. Vital Signs

The actual value and derived change from Baseline to each protocol-specified scheduled visit/time point will be summarized for each vital sign test including Weight, Body Mass Index, Respiration Rate, Temperature, Pulse Rate, Oxygen Saturation, Pulse Oximeter, Systolic Blood Pressure, and Diastolic Blood Pressure.

A subject data listing containing all vital signs data, including vital signs clinical significance, will be provided.

3.4.4. 12-Lead Electrocardiograms (ECG)

ECG parameters (heart rate [HR], PR interval [PR], RR interval [RR], QRS complex [QRS], QT interval [QT], Fridericia's corrected QT interval [QTcF] and Bazett's corrected QT interval [QTcB] intervals) will be summarized descriptively in summary tables as actual and change from baseline by treatment group for all timepoints.

ECG results (HR, PR, RR, QRS, QT, QTcF, QTcB, and classification of Normality, Abnormality with Clinical Significance, or Abnormality without Clinical Significance) will be presented in data listing

3.4.5. Physical Examinations

A subject data listing containing all Physical Examinations data will be provided.

3.4.6. Chest X-rays

Chest X-ray qualitative results will be summarized descriptively by visit/time point.

A subject data listing containing all Chest X-ray data will be provided.

3.5. Pharmacodynamic (PD) Analysis

3.5.1. Mucin Measurements

Mucin 5AC (MUC5AC) and mucin 5B (MUC5B) protein concentrations will be assessed in induced sputum, BALF, bronchosorption, and airway swab samples. Actual value and derived change from Baseline to each protocol-specified scheduled visit/time point will be summarized for MUC5AC and MUC5B. Additionally, derived MUC5AC/MUC5B ratio will be summarized by actual value and change from Baseline to each protocol-specified scheduled visit/time point.

MUC5AC and MUC5B mRNA expression will be assessed in induced sputum samples and BALF samples. Actual value and derived change from Baseline to each protocol-specified scheduled visit/time point will be summarized for MUC5AC and MUC5B mRNA expression.

Subject data listings containing mucin measurements will be provided.

3.5.2. Fractional Exhaled Nitric Oxide (FeNO)

FeNO assessments will be collected from subjects in the asthma and COPD cohorts. The actual value and derived change from Baseline to each scheduled visit/time point will be summarized. For each FeNO assessment, repeated measurements (up to six) will be collected until two measurements that agree within 10% of each other are achieved. The average of the two reproducible measurements will at each visit/time point will be used for analysis.

A subject data listing containing FeNO data will be provided.

3.5.3. Blood Eosinophil or Neutrophil Count, Serum Total IgE, Plasma Periostin

For subjects in the asthma and COPD cohorts, actual value and derived change from Baseline to each protocol-specified scheduled visit/time point will be summarized for Blood Eosinophil or Neutrophil Count, Serum Total IgE, and Plasma Periostin.

Subject data listings containing these assessments will be included with the associated clinical lab listings.

3.6. Efficacy Analysis

3.6.1. Spirometry

For NHV cohorts, spirometry assessments will be performed without bronchodilation. For asthma and COPD cohorts, the first spirometry assessment performed for each study visit will include both pre- and post-bronchodilation measures; all other spirometry assessments will be performed without bronchodilation. When assessments are performed maneuvers will be repeated (up to 8 times) in an attempt to achieve 3 acceptable FEV1 and FVC measurements.

“Acceptable” criteria are defined in a separate document detailing the Over-Reading procedure. Assessments will be transmitted to a central vendor for quality review (over-reader) where the

maneuvers and overall Spirometry session will be graded as Accepted (Passed Quality Assurance [QA]) or Rejected (Failed QA). The best prebronchodilator and the best postbronchodilator FEV1 and FVC from a given spirometry assessment will be used for analysis and sessions that are graded as Rejected will be excluded. The analysis will be repeated and sessions that are graded as Rejected will be included.

The actual value and derived change from Baseline to each protocol-specified scheduled visit/time point will be summarized for spirometry tests including: FEV1, FVC, predicted FEV1 (FEV1P), percent predicted FEV1 (FEV1PP), predicted FVC (FVCP), percent predicted FVC (FVCP), FEV1/FVC ratio (FEV1FVC), predicted FEV1/FVC ratio (FEV1FVCP), percent predicted FEV1/FVC ratio (FEV1FVCP) and FEF25-75. For subjects in the asthma and COPD cohorts, prebronchodilator and postbronchodilator spirometry tests will be summarized separately.

A subject data listing containing all spirometry data will be provided.

3.6.2. Mucus Symptom Assessments

For subjects in the asthma cohorts, Mucus Symptom Assessment qualitative results will be summarized descriptively by visit/time point.

A subject data listing containing Mucus Symptom Assessment data will be provided.

3.6.3. COPD Assessment Test (CAT)

For subjects in the COPD cohorts, CAT questionnaire results will be summarized descriptively by visit/time point.

A subject data listing containing CAT result data will be provided.

3.6.4. SGRQ-C

SGRQ-C is a self-administered questionnaire that measures health status in 3 domains: symptoms, activity, and impact. Scores for each domain and total score will be summarized descriptively by visit/time point.

A subject data listing containing SGRQ-C score will be provided.

3.7. Pharmacokinetic (PK) Analysis

PK parameter estimation and reporting will be performed by Arrowhead Pharmaceuticals, Inc., and provided as a standalone report (PK Report) for inclusion in the clinical study report (CSR).

Listings of PK concentrations and parameters by individual will be provided. PK listings will be presented using the safety population, and subjects not included in the PK population will be distinguished. Subjects without any estimable PK parameters will not be presented in the listing of PK parameters.

Summary tables and figures will be generated by Arrowhead Pharmaceuticals, Inc. and provided in the standalone PK Report. PK tables, figures, and all statistical analyses will be presented using the PK population.

3.7.1. Pharmacokinetic Profile Exclusions

Where subjects experience issues pertaining to a specific dose of ARO-MUC5AC over the duration of the study which may affect exposure to study drug during the affected visit, individual PK profiles will be reviewed and evaluated by the study pharmacokineticist on a case-by-case basis for exclusion from treatment summaries and/or the PK population. All exclusions will be documented throughout the affected data listings.

3.7.2. Below the Limit of Quantification

PK concentrations that are below the limit of quantification (BLQ) will be treated as zero for calculation of concentration descriptive statistics. For estimation of PK parameters, plasma concentrations that are BLQ will be treated as zero except for embedded BLQ samples present between 2 quantifiable concentrations. In this case, the embedded BLQ concentrations will be treated as missing. For plasma PK, should two BLQ values occur in succession after C_{max} , the profile is deemed to have terminated at the first BLQ value, and any subsequent concentrations are omitted from PK calculations. Additionally, plasma concentrations that are BLQ will be excluded from semilogarithmic plots.

3.7.3. Missing Data

All missing concentration data will be presented as missing in concentration data listings and excluded from the estimation of concentration summary statistics. For the estimation of PK parameters, the following imputations will be made:

Missing predose concentrations observed before administration of the initial dose will be imputed as zero.

Otherwise, missing results will be treated as missing and not imputed.

3.7.4. Predose Samples Collected Postdose

Predose samples collected in error after dosing will be excluded from the calculation of concentration summary statistics and included in the estimation of PK parameters using the actual time relative to dosing.

3.7.5. Summary Statistics

Summary statistics to be presented for each output are as follows:

- PK concentrations: N, number of observations (n), arithmetic mean, standard deviation (SD), geometric mean, coefficient of variation (CV), median, minimum, and maximum.
- PK parameters: N, n, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum. T_{max} will be summarized using number of observations, median, minimum, and maximum only.

Where two or fewer observations are observed (ie, $n \leq 2$), standard deviations will not be reported in tables of summary parameters.

3.7.6. PK Concentrations

Plasma PK collections that have an actual sampling time that deviates from the predefined collection time windows as defined in the study protocol will be flagged in the data listing and excluded from the calculation of concentration summary statistics.

Individual plasma and urine concentrations will be presented in data listings and summarized separately by cohort and timepoint.

Individual PK concentration versus time profiles will be presented graphically using the safety population, and subjects/profiles not included in treatment summaries and/or the PK population will be distinguished. Individual plasma concentrations will be plotted by actual time postdose on both linear and semilogarithmic scales, separated by cohort, with dosing occasions overlaid as appropriate. Mean plasma concentration versus nominal time postdose profiles will be plotted on both linear and semi logarithmic scales, with cohorts overlaid on the same plots as applicable, separated by dosing occasion.

3.7.7. PK Parameters

Plasma and urine ARO-MUC5AC concentrations from NHVs will be analyzed using noncompartmental analysis. The following plasma PK parameters will be calculated as applicable, where data permit, using the actual sampling times relative to dosing:

- Maximum observed plasma concentration ($C_{\max}$)
- Time of observed maximum plasma concentration ($T_{\max}$)
- AUC from time 0 to the last quantifiable plasma concentration (AUC_{0-t})
- AUC from time 0 extrapolated to infinity ($AUC_{0-\infty}$)
- Elimination half-life ($t_{1/2}$)
- Apparent systemic clearance (CL/F)
- Apparent terminal-phase volume of distribution (V_Z/F)

The following urine PK parameters will be calculated as applicable:

- Recovery of unchanged drug in urine over 0 to 24 hours (amount excreted; A_e)
- Percentage of the administered drug recovered in urine over 0 to 24 hours postdose
- Renal clearance (CL_R)

Additional PK parameters may be estimated as appropriate. Urine and plasma ARO-MUC5AC PK parameters will be listed and summarized descriptively. The plasma PK parameters ($C_{\max}$, AUC_{0-t} , and $AUC_{0-\infty}$) from the Single-Dose NHV cohorts 1a-4a will be analyzed for dose proportionality via a power function regression analysis. Urine metabolite concentrations will be analyzed as appropriate.

4. CHANGE FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

As of this date, there have been no changes between the protocol-defined statistical analyses and those presented in this statistical plan. Of note, immunogenicity assessments were not done.

5. PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. Detailed programming specifications will be provided in a separate document.