Statistical Analysis Plan

Investigational Product:	ARO-AAT
Protocol Title:	A Pilot Open Label, Multi-dose, Phase 2 Study to Assess the Safety and Efficacy of ARO-AAT in Patients with Alpha-1 Antitrypsin Deficiency Associated Liver Disease (AATD)
Study Number:	AROAAT-2002
Sponsor:	Arrowhead Pharmaceuticals, Inc. 177 East Colorado Boulevard, Suite 700 Pasadena, CA 91105 USA
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Protocol Version:	7.0
SAP Version:	2.1
SAP Approval Date:	28 OCT 2024

Signature Page

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

Signature **Date**

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Version Number	Date (DDMMYYYY)	Summary of Changes
Original (v1.0)	03MAY2022	NA
Amendment 7 (v2.0)	08FEB2024	• Updated from Protocol Amendment 6 to Amendment 7 • Update section 3.7.5 related to PFT data to clarify the Protocol Amendment 6 to 7 pre- and post-bronchodilation for spirometry assessments • Appendix A filled out for completion of entire study scope
Amendment 7 (v2.1)	28OCT2024	Additional liver biopsy parameters are added for consistency with the histology manual.

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List of abbreviations and definitions of terms

Abbreviation or Term	Definition/Explanation
AAT	Alpha-1 antitrypsin
AATD	Alpha-1 antitrypsin deficiency
ALT	Alanine aminotransferase
APRI	AST to Platelet Ratio Index
AST	Aspartate transaminase
CRF	Case Report Form
DLCO	Carbon Monoxide Diffusing Capacity
FEV1	1 second Forced Expiratory Volume
FIB4	Fibrosis-4 score
GGT	Gamma glutamyl transferase
ICH	International Conference on Harmonisation
ISR	Injection Site Reaction
mmHg	millimeters of mercury
MRE	Magnetic Resonance Elastography
MRI	Magnetic Resonance Imaging
MRI-PDFF	Magnetic Resonance Imaging Proton Density Fat Fraction
PD	Pharmacodynamic
RNAi	RNA interference
siRNA	Short interfering RNA oligonucleotides
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
ULN	Upper Limit of Normal
Z-AAT	Mutant AAT protein from Z allele

1. INTRODUCTION

This statistical analysis plan (SAP) is designed in compliance with ICH E9 to outline the methods to be used in the analysis of study data in order to evaluate the study objective(s) from Arrowhead Pharmaceuticals, Inc. (Sponsor) protocol AROAAT-2002 Version 7.0, dated 21 Jul 2022. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

An approved and signed SAP is required prior to database lock.

The formats for the tables, figures, listings (TFLs) described in this SAP are provided in a companion document. A table of contents for the TFLs will be included.

2. STUDY OVERVIEW

2.1 Endpoints

Primary Endpoint:

- To evaluate change from baseline over time in total, soluble, and insoluble Z-AAT concentrations in the liver of patients with AAT-associated liver disease.

Secondary Endpoints:

- To determine the effect of multiple doses of ARO-AAT on circulating levels of Z-AAT alpha-1 antitrypsin over time versus baseline.
- To evaluate the effect of ARO-AAT on changes in ALT over time.
- To evaluate the effect of ARO-AAT on changes in GGT over time.
- To evaluate the effect of ARO-AAT on changes in FIB4 and APRI over time.
- To evaluate the effect of ARO-AAT on changes in PRO-C3 over time.
- To evaluate the effect of ARO-AAT on changes in hepatic stiffness based on FibroScan® over time versus baseline (when available).
- To evaluate effect of ARO-AAT on histological metrics of liver disease in patients with AAT-associated liver disease over time.
- To evaluate change from baseline in Metavir fibrosis score over time in ARO-AAT treated patients.
- To determine the incidence and severity of adverse events as a measure of the safety and tolerability of ARO-AAT.
- Incidence of anti-drug antibodies to ARO-AAT

Exploratory Endpoints:

- To evaluate the effect of ARO-AAT on changes in hepatic stiffness based on Magnetic Resonance Elastography (MRE) over time versus baseline (optional).
- To evaluate changes in hepatic *SERPINA1* mRNA expression over time versus baseline in response to multiple doses of ARO-AAT (if sufficient sample available).
- To evaluate changes in liver disease related gene expression over time versus baseline (if scientifically feasible and sufficient sample available).
- To evaluate change in liver PAS+D stained globule size and number over time versus baseline.
- To evaluate the effect of ARO-AAT on changes in liver collagen using biomarkers (e.g. Pro-C6), special stains and imaging [Masson's Trichrome, Sirius Red, Iron] (if scientifically feasible and sufficient sample available) over time versus baseline.
- To determine the effect of multiple doses of ARO-AAT on circulating levels of total alpha-1 antitrypsin at multiple post-dose time points versus baseline (**patients on and not on** AAT augmentation therapy will be evaluated separately).
- Any data-driven exploratory endpoint

2.2 Study Design

2.2.1 Overview

This is a multi-center, multi-dose, open-label, Phase 2 study conducted to evaluate the safety and efficacy of the investigational product, ARO-AAT, administered subcutaneously to patients with Alpha-1 Antitrypsin Deficiency.

The study will include 3 study periods: 1) a Primary Study Period, 2) an optional Treatment Extension I, and 3) an optional Treatment Extension II, which are described below.

Primary Study Period (6-12 Months)

Participants who have signed an IRB/EC approved informed consent and have met all the protocol eligibility criteria during Screening, will be enrolled in one of three cohorts:

- **Cohort 1**: 200 mg dose of subcutaneous ARO-AAT
- **Cohort 1b**: 100 mg dose of subcutaneous ARO-AAT
- **Cohort 2**: 200 mg dose of subcutaneous ARO-AAT

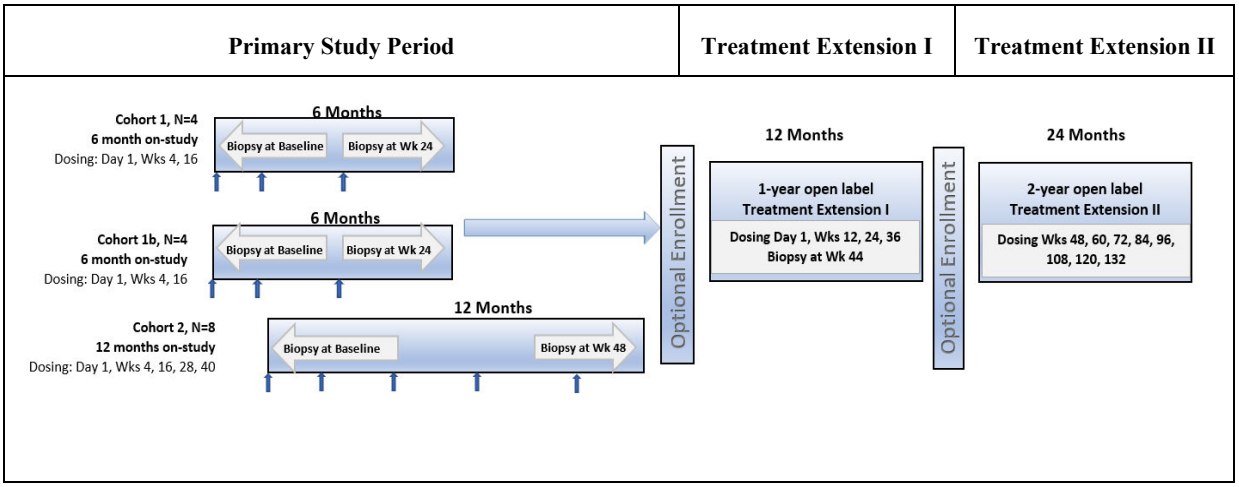
Cohorts 1 and 1b will receive a minimum of 3 doses and Cohort 2 will be receiving a minimum of 5 doses. All subjects will have a baseline biopsy and post-baseline biopsy at Week 24 (Cohorts 1 and 1b) OR at Week 48 (Cohort 2) per the Schedule of Assessments, OR at Early Termination. At the end of the Primary Study Period, subjects will be offered the opportunity to continue treatment in the open-label Treatment Extension I. Participants who drop out prior to biopsy at the end of the Primary Study Period for reasons other than an AE considered at least possibly related to drug, may be replaced.

Treatment Extension I (12 Months)

Subjects who opt to continue in Treatment Extension I will receive the same dose level of ARO-AAT as administered in their assigned initial cohort every 12 weeks (Q12W). Dosing with ARO-AAT may continue approximately 12 weeks from the previous dose in the Primary Study Period. All subjects who opted to continue will have a biopsy at Week 44 of Treatment Extension I. At the end of this study period, subjects may opt to continue treatment for up to an additional 24 months in Treatment Extension II.

Treatment Extension II (up to 24 Months)

Subjects will continue to receive the same dose level of ARO-AAT Q12W for up to an additional 24 months or until they roll over into another long-term Extension study, whichever comes first. Dosing with ARO-AAT may continue approximately 12 weeks from the previous dose in Treatment Extension I. No biopsies will be collected in Treatment Extension II.



2.2.2 Randomization and Blinding

This is an open label study, and no randomization is conducted.

3. STATISTICAL METHODOLOGY

3.1 General Considerations

Tabulations will be produced for appropriate demographic, baseline, efficacy, pharmacodynamics, and safety parameters.

Descriptive statistics on categorical variables will be reported using frequencies and percentages. All percentages will be presented with one-decimal point. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies, but the categories whose counts are zero will be displayed for the sake of completeness.

Descriptive statistics on continuous variables will be summarized using the mean, median, standard deviation, minimum and maximum values. The same number of decimal places as in the raw data will be presented when reporting min and max, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD.

Considering subjects from cohort 1 and cohort 2 will receive 200 mg dose of AROAAT but different schedule of assessment and subjects from cohort 1b will receive 100 mg dose of AROAAT, analyses will be broadly displayed by cohorts (cohort 1b, cohort 1, cohort 2) and dose level (100 mg and 200 mg) without specification. All data will be summarized as observed except specify otherwise

3.1.1 Hypothesis testing

No formal hypothesis is considered for this open label study. The analysis will be descriptive in nature.

3.1.2 Definitions

Baseline: Baseline value is defined as the latest non-missing value measured prior to the first dose of investigational product.

TEAE: treatment emergent adverse event is defined as adverse event first occurred or worsened in severity following IP administration through EOS or early termination whichever is earlier.

TESAE: treatment emergent serious adverse event is defined as adverse event first occurred or worsened in severity following IP administration through EOS or early termination whichever is earlier.

Analytical Day: Since each cohort has different schedule of assessment and there are multiple treatment periods involved in this study. By visit analyses will be displayed using analytical day described in Appendix A.

FIB-4: FIB-4 is calculated as

$$FIB4 = \frac{Age\ (yr) * AST(U/L)}{Platelet\ Count(10^9/L) * \sqrt{ALT(U/L)}}$$

APRI: APRI is calculated as

$$APRI = \frac{\frac{AST(U/L)}{AST(upper\ limit\ of\ normal\ U/L)}}{Platelet\ Count(10^9/L)}$$

Injection site reaction (IRS): AEs at the injection site is captured in eCRF.

3.1.3 Handling of Missing and Incomplete Data

Subjects maybe missing specific data points for various reasons. In general, data may be missing due to a subject's early withdrawal from study, a missed visit or non-evaluability of a data point or an endpoint at a particular point in time. Queries will be made to the sites to distinguish true missing values from other unknown values (due to measurement or sample processing error). All attempts will be made to capture missing or partial data for this trial before planned analyses and database lock.

Adverse event, prior and concomitant mediation, and medical history with completely or partial missing start dates will be queried. After the issue is queried, if the date is still incomplete, the start date will be imputed as described in Table below.

Missing	Imputation	Exception
Day	01	Default to Study Day 1 if an AE, medication/procedure starts the same year and month as Study Day 1 and the end date has same year and month as Study Day 1 or later.
Day / Month	01 / Jan	Default to Study Day 1 if an AE, medication/procedure starts the same year as Study Day 1 and the end date has same year as Study Day 1 or later.
Day / Month / Year	To calculate a missing start date: 1. If a partial or complete stop date is present:	

	a. Stop date < first dosing date: impute January 1 of the stop year b. Stop date ≥ first dosing date: impute the date of first dose 2. If it is unknown whether the stop date is < or ≥ first dosing date due to a missing or partial stop date, or if a stop date is not collected: impute date of first dose.	

Medications and procedures with missing or partial end dates will be assumed to be concomitant unless a partial end date documents it as ending prior to treatment.

The original missing or partial date, the imputed complete date, and an indicator variable that indicates which dates were imputed will be retained in the database. Dates will be presented as collected in all listings. Imputed dates will not be presented in listings but may be used for summary tables.

3.1.4 Outliers

Descriptive statistics may be used to identify outliers of key variables. However, no statistical analysis or adjustment for outliers is planned; outliers will not be omitted from summaries.

3.2 Analysis Sets

Safety Analysis Set

Safety Analysis Set includes all subjects who receive at least one dose of study drug. The Safety Analysis Set will be used for safety endpoints, pharmacodynamics endpoints and efficacy endpoints.

Full Analysis Set (FAS):

Full Analysis Set includes all subjects who receive at least one dose of study drug and have baseline and post-dose liver biopsy histology results available. FAS population will be used for all efficacy analyses.

Per Protocol (PP) Set:

Per Protocol (PP) Set includes all FAS patients who did not violate the protocol in a substantial manner, such determination to be made prior to database lock.

3.3 Covariates and Subgroups

Not applicable

3.4 Subject Data and Study Conduct

3.4.1 Subject Disposition

The number and percentage of subjects received investigational product, completed study and discontinued study (primary reasons for early termination) will be summarized using Safety Analysis Set. Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented.

3.4.2 Protocol Deviations

The number and percentage of randomized subjects with important protocol deviations will be summarized by deviation category and by as-randomized treatment group and overall. Deviation categories will be presented in descending order of overall frequency.

A by-subject listing of protocol deviations will be provided for enrolled subjects. The Safety Analysis Set will be used to summarize protocol deviations.

3.4.3 Demographic and Baseline Characteristics

Demographics data will include:

- Age (in years), also categorized as < 50, 50-65, ≥ 65
- Sex (male, female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (American Indian or Alaska Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other, Not Reported, Unknown)

Baseline characteristics and disease history include:

- Weight (kg)
- Height (cm)
- BMI (kg/m2)
- Subject has past medical conditions (yes, no)
- Subject has smoking history (yes, no)
- Subject smoked cigarettes/e-cigarettes within the past 12 months (yes, no)
- Fibrosis score at baseline (central reading)
- FEV1 at baseline
- Percent predicted FEV1 at baseline
- PiZZ genotype confirmed (yes, no)
- On AAT augmentation therapy (yes, no)
- Gilbert's Syndrome (yes, no)

3.4.4 Medical History

Medical history will be summarized by system organ class (SOC) and preferred term (PT), and displayed in descending order of overall frequency within SOC and PT.

A by-subject listing of medical history will be provided based on Safety Analysis Set.

3.4.5 Concomitant Medication

Concomitant medications will be defined as all medications taken by the patient any time on-study treatment or within 28 days after the last administration date of investigational product. Prior medications will be defined as all medications taken by the patient before the first injection of the study drug.

Prior and concomitant medications will be coded using the WHO-DD. Results will be tabulated alphabetically by Anatomic Therapeutic Class (ATC) and Preferred Name. For each subject, multiple records of the same medication will be counted only once within each ATC and/or Preferred Name.

In case the date value does not allow allocation of a medication to prior or concomitant category, the medication will be considered as concomitant.

Concomitant and prior medications will be summarized using data recorded in the "Concomitant Medications/Therapies" eCRF pages.

A by-subject listing of concomitant medications/therapies will be provided. Prior and concomitant medications will be flagged.

3.4.6 Investigational Product Exposure

Study drug exposure will be summarized descriptively by treatment group for treated subjects, and will include the following parameters:

- Total number of injections received
- Duration of study follow-up (weeks)
- Number and percentage of subjects in the following duration of study follow-up categories: 0 to 24 weeks, >24 to 48 weeks, >48 to 72 weeks, >72 weeks

3.5 Efficacy Analyses

Analysis of efficacy endpoints will be based on Full Analysis Set.

3.5.1 Liver Z-AAT protein

Descriptive statistics and derived change from baseline and percent change from baseline in insoluble Z-AAT protein, soluble Z-AAT protein and total Z-AAT protein will be summarized. Owing to the limited sample size of each cohort, changes from baseline may be tested using non-parametric Wilcoxon signed-rank test for significance due to data availability.

For measurement of intra-hepatic Z-AAT below the detection limit, half of the lower limit value will be imputed for summaries.

A by-subject liver Z-AAT listing will be provided. Listing won't include imputed values.

3.5.2 **Liver Biopsy**

For METAVIR fibrosis score, a descriptive statistics summary displaying the number and percent of subjects having ≥ 1-point improvement from baseline, no change from baseline, and ≥ 1-point worsening from each of the baseline category will be generated. A shift table of METAVIR fibrosis score (F0–F4) from baseline to post-baseline (F0-F4) score will be presented.

Similarly, percent of subjects having improvement from baseline, no change from baseline and worsening from each of the baseline category in following liver biopsy parameters will be summarized.

- PAS+D Globule Burden (0-9) (Sum of Globule Portal Tract Involvement, Periportal Hepatocyte Involvement, and Zonal Location).
- Globule Portal Tract Involvement (0-3)
- PAS+D Zonal Location (0-3)
- Zone 1 Globule Periportal Involvement (0-3)
- Globule Burden of Globules > RBC (0-3)
- Globule Size (0-3)
- Portal Inflammation (0-3)
- Interface Hepatitis (0-3)
- Lobular Inflammation (0-3)
- Hepatocyte Cell Death (0-2)
- Steatosis (0-3)
- Brunt Macrovascular Steatosis Score (0-3)
- Hepatocellular Ballooning (0-3)
- NASH Diagnosis (0-3)
- ISHAK Fibrosis (0-6)
- Ductular Reaction (0-2)
- Iron Deposition (0-4)
- Periportal Lipofuscin (0-1)
- AATD Liver Disease Severity (0-3)

PAS+D Globule Burden includes portal tract involvement, periportal hepatocyte involvement and zonal location. Each give a score 0-3, equal weight will be assigned and calculated the total aggregate score 0-9. Descriptive statistics and change from baseline in PAS+D Globule Burden will be also summarized.

In addition, overall shift table of METAVIR score, PAS+D globule burden, portal inflammation, interface hepatitis, hepatocyte cell death and lobular inflammation will be provided. The number and percent of subjects having ≥ 1-point improvement from baseline, no change from baseline, and ≥ 1-point worsening from baseline will be summarized based on eligible baseline scores. For example, if 3 out of 4 subjects have portal inflammation improve and only these 3 subjects have

baseline scores more than 0 and the other subject has baseline score as 0, the percent of improvement will be calculated as 3 out of 3, which is 100%. The denominator of this overall summary will be the number of subjects who are eligible to meet the improvement or worsening condition.

A by-subject listing will be provided to present liver biopsy data.

3.6 Analyses of Pharmacodynamic Endpoints

Analyses of pharmacodynamic endpoints will be based on Safety Analysis Set.

Serum ZAAT protein

Descriptive statistics and derived change from baseline and percent change from baseline in serum ZAAT will be summarized. The change from baseline in serum Z-AAT may be tested by non-parametric Wilcoxon signed-rank test at scheduled visit.

A by-subject serum Z-AAT listing will be included.

Longitudinal plots of serum Z-AAT and percent change in serum Z-AAT will be generated.

Serum Fibrosis and Imaging Markers

Descriptive statistics and derived change from baseline and percent change from baseline in following PD parameters will be provided

- FIB4 and APRI
- PRO-C3
- Hepatic stiffness (FibroScan)

The derivation of FIB4 and APRI refer to Section 3.1.2 Definition.

Descriptive statistics and change from baseline of MRE may be summarized based on data availability.

3.7 Safety Analyses

Safety data will be summarized using Safety Analysis Set.

3.7.1 Adverse Events

All AEs and SAEs will be collected and reported in the patient's eCRF throughout study duration, i.e., from the first trial related activity after the subject signs the informed consent and until EOS.

The Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

An overall summary of AEs will be provided. The overall summary will include the number and percentage of subjects reporting at least one: TEAE; mild TEAE; moderate TEAE; severe

TEAE; TEAE possibly related to study drug; TEAE probably related to study drug; TESAE; TEAE leading to study drug discontinuation; TEAE leading to study termination; and deaths.

Subject incidence of all treatment-emergent adverse events, treatment-emergent serious adverse events, treatment-emergent treatment related adverse events, treatment-emergent adverse events leading to discontinuation of investigational product, fatal adverse events and injection site reaction will be tabulated by system organ class and preferred term in alphabetical order.

Subject incidence of all treatment-emergent adverse events, treatment-emergent serious adverse events will be tabulated by preferred term in descending order of frequency.

Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class, preferred term, and grade.

A by-subject listing of all AEs reported in the eCRF will be provided. Duration of AE (i.e., AE end date – AE start date + 1) will be included in the listing. Separate listings will be presented for all SAEs, deaths, and injection site reaction AEs.

3.7.2 Laboratory Test Results

Laboratory data including biochemistry, hematology, coagulation and urinalysis will be summarized using descriptive statistics at each scheduled timepoint in study. For continuous parameters, a summary of the change from baseline and percent change from baseline to each post dose laboratory assessment will be produced. Shifts in selected laboratory parameters including ALT, AST, alkaline phosphatase, CK, GGT, total bilirubin, and INR between baseline and the worst on-study value will be summarized by NCI CTCAE toxicity grades. The number and percent of subjects will be reported in each shift category.

Separate summary table will be generated for lab parameters of interests, but not limited to, ALT, AST, alkaline phosphatase, CK, GGT, total bilirubin. Longitudinal plots of these laboratory parameters by visit and treatment group will be generated as well. An evaluation of drug-induced serious hepatotoxicity (eDISH) scatter plot will be produced. Maximum total bilirubin (presented as xULN) will be plotted on a log scale on the y-axis and maximum ALT (presented as xULN) will be plotted on a log scale on the x-axis. A horizontal reference line will be placed at 2x ULN for maximum total bilirubin, and a vertical reference line will be placed at 3x ULN for maximum ALT. The lower left quadrant will be labeled “Normal Range”. The upper left quadrant will be labeled “Cholestasis Quadrant”. The lower right quadrant will be labeled “Temple’s Corollary Quadrant”. The upper right quadrant will be labeled “Hy’s Law Quadrant”.

All laboratory data will be provided in data listings. A subset listing will be presented for all clinically significant abnormal laboratory values. This listing will present all lab values for any parameter with at least one clinically significant abnormal value so that a time course for that lab parameter can be presented.

3.7.3 Vital Signs and Physical Measurements

Vital signs include body temperature (°C), heart rate (beats/min), respiratory rate (breaths/min), systolic and diastolic blood pressures (mmHg). Physical measurements include height (cm, measured only at baseline), weight (kg), and BMI (kg/m2).

The observed value and change from baseline in vital signs and physical measurements will be summarized at each visit. A by-subject listing will be provided as well.

3.7.4 Electrocardiogram

ECG parameters will include heart rate (beats/min), PR interval, QRS interval, QT interval, and QTcF interval.

The observed value and change from baseline in ECG parameters will be summarized as continuous variables at baseline and each post-baseline visit.

ECG interpretation shift from baseline to each post-baseline timepoint will be summarized as the number and percentage of subjects with normal, clinically insignificant abnormal, and clinically significant abnormal interpretations.

By-subject listing of ECG data will be provided and repeat ECGs will be flagged.

3.7.5 Pulmonary Function

Descriptive statistics and the derived change from baseline and percent change from baseline in FEV1(L), VC(L), FVC (L), DLCO (mL/min/mmHg) and DLCO adjusted for hemoglobin(mL/min/mmHg) will be provided by the scheduled study visit. Descriptive statistics and the derived change from baseline in percent predicted FEV1, percent predicted VC, percent predicted FVC, percent predicted DLCO and percent predicted DLCO adjusted for hemoglobin will be provided by the scheduled study visit.

DLCO adjusted for hemoglobin is defined as below

$$DLCO_{hgb}(Male\ and\ age \geq 15\ yr) = DLCO\ (10.22 + Hgb)/(1.7 * Hgb)$$

$$DLCO_{hgb}(Femable\ or\ age < 15\ yr) = DLCO(9.38 + Hgb)/(1.7 * Hgb)$$

where Hgb is the value of hemoglobin collected same day as measurement of DLCO.

Proportion of subject who meet following pulmonary function decline will be summarized by each schedule visit.

- Decline from baseline in FEV1 ≥ 200 ml, ≥ 300ml, ≥10%, ≥ 15%
- Decline from baseline in FVC ≥ 200 ml, ≥ 300ml, ≥10%, ≥ 15%
- Decline from baseline in DCLO ≥ 6.5 ml/(min*mmHg), ≥10%, ≥ 15%
- Decline from baseline in DCLO adjusted for hemoglobin ≥ 6.5 ml/(min*mmHg), ≥10%, ≥ 15%

PFT data will be summarized by baseline augmentation status Yes vs No and overall.

Longitudinal plots of PFT parameters (FEV1, FVC and DLCO adjusted and unadjusted for hemoglobin) and change from baseline in percent predicted PFT parameters will be generated.

A by-subject listing of pulmonary function test results will be provided.

The number of patients that require augmentation treatment at any time throughout the study will be summarized. Time from baseline to initiation of augmentation therapy maybe summarized using Kaplan Meier estimates due to data availability.

After Protocol Amendment 7, PFT text was updated to clarify instructions for performing spirometry, to acknowledge acceptability of following bronchodilator administration as per site practice. See protocol section 9.3.4 from Amendment 6 "*All spirometry and DLCO values recorded will be those completed post-bronchodilation (unless contraindicated or unavailable).*" vs. Amendment 7 "*All spirometry and DLCO values collected and recorded will include both pre- and post-bronchodilation measurements [unless contraindicated or unavailable]*.". Thus, for spirometry assessments (FEV1, VC, FVC), in addition to summarizing pre- and post-bronchodilation measurements separately, additional summaries will be provided where post-bronchodilation measurements are used when available and pre-bronchodilation measurements are used in the absence.

3.8 Analysis of Immunogenicity

Immunogenicity will be assessed for anti-drug antibodies. Results will be described by frequency tables on patients with presence of anti-drug antibodies, by time of assessment using Safety Analysis Set.

Summary statistics for changes from baseline in detected levels of anti-drug antibodies will be calculated and presented.

Immunogenicity data will be provided in a by-subject listing.

4. SAMPLE SIZE DETERMINATION

No formal sample size calculations were conducted in this open label exploratory study.

5. PLANNED ANALYSES

5.1 Interim Analysis and Early Stopping Guidelines

No formal interim analysis is planned for this study. Since this is an open label study, ad hoc interim analyses maybe performed depending on business need. Ad hoc interim analyses will be descriptive in nature.

5.2 Final Analysis

The Final Analysis will be performed once all subjects complete the last visit or early termination whichever is earlier and after database lock. Data will be cleaned, and all queries will be addressed before database lock.

6. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There have been no changes between the Protocol AROAAT2002 V7.0 defined statistical analyses and those presented in this statistical plan.

7. LITERATURE CITATIONS/REFERENCES

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8. APPENDIX

8.1 Appendix A: Analytical Day

Analytical Day for cohort 1 and cohort 1b

Study Period	Visit	Analytical Day
Primary (3 DOSES)		
	Screening	Screening
	Day 1 *	Day 1 *
	Day 2 (24-48 hr) PSD	Day 2 (24-48 hr) PSD
	Wk 2	Wk 2
	Wk 4 *	Wk 4 *
	Wk 4 (24-48 hr) PSD	Wk 4 (24-48 hr) PSD

	Wk 6	Wk 6
	Wk 16 *	Wk 16 *
	Wk 16 (24-48 hr) PSD	Wk 16 (24-48 hr) PSD
	Wk 24	Wk 24
	12 Wk Post Last Dose	Wk 28
Extension I (4 DOSES)		
	Day 1 *	Wk 28 + 1 day *
	Wk 6	Wk 34
	Wk 12 *	Wk 40 *
	Wk 18	Wk 46
	Wk 24 *	Wk 52 *
	Wk 30	Wk 58
	Wk 36 *	Wk 64 *
	Wk 44	Wk 72
Extension II (8 DOSES)		
	Wk 48 *	Wk 76 *
	Wk 54	Wk 82
	Wk 60 *	Wk 88 *
	Wk 66	Wk 94
	Wk 72 *	Wk 100 *
	Wk 78	Wk 106
	Wk 84 *	Wk 112 *
	Wk 92	Wk 120
	Wk 96 *	Wk 124 *
	Wk 104	Wk 132
	Wk 108 *	Wk 136 *
	Wk 116	Wk 144
	Wk 120 *	Wk 148 *
	Wk 128	Wk 154
	Wk 132 *	Wk 160 *

	Wk 140	Wk 168

Analytical Day for cohort 2

Study Period	**Visit**	**Analytical Day**
Primary (5 DOSES)		
	Screening	Screening
	Day 1 *	Day 1 *
	Day 2 (24-48 hr) PSD	Day 2 (24-48 hr) PSD
	Wk 2	Wk 2
	Wk 4 *	Wk 4 *
	Wk 4 (24-48 hr) PSD	Wk 4 (24-48 hr) PSD
	Wk 6	Wk 6
	Wk 16 *	Wk 16 *
	Wk 16 (24-48 hr) PSD	Wk 16 (24-48 hr) PSD
	Wk 22	Wk 22
	Wk 28 *	Wk 28 *
	Wk 34	Wk 34
	Wk 40 *	Wk 40 *
	Wk 48	Wk 48
	12 Wk Post Last Dose	Wk 52
Extension I (4 DOSES)		
	Day 1 *	Wk 52 + 1 day *
	Wk 6	Wk 58
	Wk 12 *	Wk 64 *
	Wk 18	Wk 70
	Wk 24 *	Wk 76 *
	Wk 30	Wk 82
	Wk 36 *	Wk 88 *
	Wk 44	Wk 96
Extension II (8 DOSES)		

	Wk 48 *	Wk 100 *
	Wk 54	Wk 106
	Wk 60 *	Wk 112 *
	Wk 66	Wk 118
	Wk 72 *	Wk 124 *
	Wk 78	Wk 130
	Wk 84 *	Wk 136 *
	Wk 92	Wk 144
	Wk 96 *	Wk 148 *
	Wk 104	Wk 154
	Wk 108 *	Wk 160 *
	Wk 116	Wk 168
	Wk 120 *	Wk 172 *
	Wk 124	Wk 176
	Wk 132 *	Wk 184 *

"*" denotes dosing day.