Statistical Analysis Plan Addendum

Investigational Product:	Fazirsiran (TAK-999, ARO-AAT)
Protocol Title:	A Placebo-Controlled, Multi-dose, Phase 2 Study to Determine the Safety, Tolerability and Pharmacodynamic Effect of Fazirsiran in Patients with Alpha-1 Antitrypsin Deficiency (AATD) [SEQUOIA]
Study Number:	AROAAT-2001
Sponsor:	Arrowhead Pharmaceuticals, Inc. 177 East Colorado Boulevard, Suite 700 Pasadena, CA 91105 USA
Protocol Version:	Version 6.0
SAP Addendum Version:	Version 1.0
SAP Approval Date:	30JAN2024

Signature Page

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

Signature **Date**

[redacted]

Arrowhead Pharmaceuticals, Inc.

DocuSigned by:
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Version Number	Date (DDMMYYYY)	Summary of Changes
Original (v1.0)	30JAN2024	N/A

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Definition
AAT	Alpha-1 antitrypsin
AATD	Alpha-1 antitrypsin deficiency
ALT	Alanine aminotransferase
AST	Aspartate transaminase
ARO	Arrowhead Pharmaceuticals, Inc
ARO-AAT Injection	Clinical drug product solution ready for SC injection
ARO-AAT	Short name for ARO-AAT Injection
BP	Blood Pressure
CRF	Case Report Form
DLCO	Carbon Monoxide Diffusing Capacity
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
FDA	Food and Drug Administration
FEV_1	1 second Forced Expiratory Volume
FSH	Follicle-Stimulating Hormone
GGT	Gamma glutamyl transferase
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISR	Injection Site Reaction
LD	Lactate Dehydrogenase
LISR	Local Injection Site Reaction
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Cell Volume
mmHg	millimeters of mercury
MRE	Magnetic Resonance Elastography
MRI	Magnetic Resonance Imaging
MRI-PDFF	Magnetic Resonance Imaging Proton Density Fat Fraction
PD	Pharmacodynamic
PBO	Placebo
PI	Principal Investigator
PiZZ	Homozygous Z allele individuals
PK	Pharmacokinetic
PT	Prothrombin Time
PTT	Partial thromboplastin time

Abbreviation	Definition
RNAi	RNA interference
SAE	Serious Adverse Event
SD	Standard Deviation
siRNA	Short interfering RNA oligonucleotides
SOA	Schedule of Assessments
TIA	Transient Ischemic Attack
ULN	Upper Limit of Normal
Z-AAT	Mutant AAT protein from Z allele

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

This document presents the statistical analysis plan (SAP) addendum for Arrowhead Pharmaceuticals, Protocol AROAAT2001: A Placebo-Controlled, Multi-dose, Phase 2 Study to Determine the Safety, Tolerability and Pharmacodynamic Effect of Fazirsiran in Patients with Alpha-1 Antitrypsin Deficiency (AATD) [SEQUOIA].

This SAP Addendum is based on the AROAAT2001, V6.0, protocol dated 29 August 2022. Per the final SAPv3.0 signed prior to study unblinding, “Data collected in an open label stage will be descriptively summarized”. The purpose of this SAP Addendum is to provide further detail on these open-label phase descriptive statistics. Analyses that were described in the final SAPv3.0 will not be described again in this document.

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

1.2. Objectives and Endpoints

Refer to SAPv3.0.

2. STUDY DESIGN

Refer to SAPv3.0.

3. SUBJECT POPULATIONS

Refer to SAPv3.0.

3.1. Population Definitions

The following population samples for analyses will be evaluated and used for presentation and analysis of data captured during the open-label phase:

- Open-label Phase Set: All subjects who receive at least one dose of Fazirsiran in the open-label phase.

4. DEFINITIONS AND DATA HANDLING

The following general data handling conventions, will be used in the derivation of variables used in summaries of the open-label phase data:

Table 1: Definitions

Term	Definition/Rule
Baseline	The latest measurement performed prior to the first dose of open-label phase Fazirsiran.
Study Day	(Date of assessment) – (date of first dose of open-label phase Fazirsiran) + 1, if date of assessment ≥ date of first dose of open-label phase Fazirsiran; (Date of assessment) – (date of first dose of open-label phase Fazirsiran), if date of assessment < date of first dose of open-label phase Fazirsiran
TEAE	Adverse event that first occurred or worsened in severity following dose administration of the first dose of open-label phase Fazirsiran through EOS or Early Termination
TESAE	Serious adverse event that first occurred or worsened in severity following dose administration of the first dose of open-label phase Fazirsiran through EOS or Early Termination

For other general definitions and data handling, refer to SAPv3.0.

5. PLANNED ANALYSIS

Refer to SAPv3.0

6. STATISTICAL METHODS OF ANALYSIS

6.1. General Considerations

Refer to SAPv3.0.

As indicated in the protocol Schedule of Assessments, select assessments continue into the open-label phase. Generally, data collected in the open-label phase will by descriptively summarized in separate summaries from those pertaining to data collected in the double-blind phase.

No separate open-label phase listings will be generated.

6.2. Efficacy Evaluation

No separate efficacy analyses will be performed.

6.3. Pharmacodynamic Evaluations

Serum Z-AAT value and derived change/percent change from baseline at each open-label visit will be summarized.

Serum Fibrosis Markers

A descriptive statistics summary of serum Pro-C3, Pro-C6, APRI and FIB-4 by open-label visit will be provided by fibrosis status at Screening. Derived changes from baseline and percent changes from baseline will be included. Subgroup analysis based on central read Metavir score will be done.

FIB-4: FIB-4 is calculated as

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

APRI: APRI is calculated as

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

6.4. Safety Analyses

Refer to SAPv3.0

6.4.1. Adverse Events

Adverse events analyses described in the SAPv3.0 will be repeated for adverse events captured during open-label phase. Overall summaries of TEAEs occurring during the double-blind phase and open-label phase will be provided. The overall summaries will include the number and percentage of subjects reporting at least one: TEAE; TESAE; TEAE by severity; treatment related TEAE; TEAE leading to study drug discontinuation; TEAE leading to study termination; inject site reaction and deaths.

Descriptive statistics summaries of subject incidence of AEs will be summarized for all TEAEs, treatment-related TEAEs, TESAEs, treatment-related TESAEs, TEAEs resulting in study drug discontinuation, TEAE with an outcome of death, TEAE at injection site, TEAE relevant to COPD exacerbation, TEAE (incidence rate ≥ 5%) by SOC in alphabetical order and PT in descending order of frequency. Subject incidence of TEAEs will also be

summarized by PT in descending order of frequency. TEAE will be summarized by fibrosis status at Screening. Number of TEAEs will be summarized by SOC in alphabetical order and PT in descending order of frequency.

Descriptive statistics summaries of subject incidence of TEAE, TEAE at injection site, by SOC, PT, severity will be provided. Subjects will be counted once under the worst severity reported within each SOC and PT.

Descriptive statistics summaries of subject incidence of TEAEs by SOC, PT and relationship to investigation product will be provided. Subjects will be counted once under the closest relationship reported within each SOC and PT.

Descriptive statistics of exposure-adjusted incidence rate of TEAES by PT will be provided. The definition of exposure-adjusted incidence rate is the number of subjects experiencing the TEAE divided by the total exposure-time among subjects, where each subject's exposure in person-year is calculated as (date of last dose of study drug – date of first dose of study drug +1) / 365.25.

6.4.2. Laboratory Data

Laboratory data (details refer to Protocol section 9.2.6), including biochemistry, hematology, and coagulation will be summarized using descriptive statistics at each open-label visit. For continuous parameters, a summary of the change from baseline and percent change from baseline to each post dose laboratory assessment in the open-label phase will be produced. Shifts in selected laboratory parameters between baseline and the worst open-label assessment value will be summarized according NCI CTCAE toxicity grades. The number and percent of subjects will be reported in each shift category.

Separate summary table will be generated for ALT, AST, alkaline phosphatase, CK, GGT, total bilirubin, direct bilirubin and INR. An evaluation of drug-induced serious hepatotoxicity (eDISH) scatter plot will be produced for the open-label phase. 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".

6.4.3. Prior and Concomitant Medication

Refer to SAPv3.0 for prior and concomitant medications.

No separate concomitant medications summaries will be generated.

6.4.4. Electrocardiogram (12-Lead ECG)

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

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

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

6.4.5. Vital Signs and Physical Measurements

Vital signs include body temperature (°C), pulse 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/m^2).

The observed value and change from baseline in vital signs and physical measurements will be summarized at each open-label stage visit.

6.4.6. Pulmonary Function

Refer to SAPv3.0 for additional details related to pulmonary function assessments.

Change from baseline in pulmonary function test parameters (PFT) will be summarized by time point for open-label phase visits. Additional plots of PFT parameters and change from baseline trend will be generated.