PROTOCOL NUMBER:	**AROAAT2002**
STUDY TITLE:	**A Pilot Open Label, Multi-dose, Phase 2 Study to Assess the Safety and Efficacy of Fazirsiran (TAK-999, ARO-AAT) in Patients with Alpha-1 Antitrypsin Deficiency Associated Liver Disease (AATD)**
DRUG (Active):	**Fazirsiran (TAK-999, also referred to as ARO-AAT) Injection**
ROUTE:	**Subcutaneous Injection**
STUDY DESIGN:	**A multi-center, multi-dose, open-label phase 2 study will be conducted to evaluate the safety and efficacy of the investigational product, fazirsiran (TAK-999, ARO-AAT), administered subcutaneously to patients with Alpha-1 Antitrypsin Deficiency.**
SPONSOR:	**Arrowhead Pharmaceuticals, Inc.** **177 East Colorado Boulevard** **Suite 700** **Pasadena, CA 91105** **Telephone: +1 626 304 3400 Facsimile: +1 626 304 3401**
EudraCT Number:	**2019-000068-86**
Version:	**7.0**

Confidential

1. PROTOCOL SYNOPSIS

Study Title: A Pilot Open Label, Multi-dose, Phase 2 Study to Assess the Safety and Efficacy of Fazirsiran (TAK-999, ARO-AAT) in Patients with Alpha-1 Antitrypsin Deficiency Associated Liver Disease (AATD)
Study Number: AROAAT2002
Phase: Phase 2
Location: Multiple sites in Europe and United Kingdom
Study Treatments: The study treatment is Fazirsiran (TAK-999, also referred to as ARO-AAT) Injection. The active pharmaceutical ingredient (API) fazirsiran is a synthetic, double-stranded, small interfering RNA (siRNA) duplex conjugated to an N-acetyl-galactosamine targeting ligand to facilitate hepatocyte delivery.
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 fazirsiran on circulating levels of Z-AAT alpha-1 antitrypsin over time versus baseline. • To evaluate the effect of fazirsiran on changes in ALT over time. • To evaluate the effect of fazirsiran on changes in GGT over time. • To evaluate the effect of fazirsiran on changes in FIB-4 and APRI over time. • To evaluate the effect of fazirsiran on changes in PRO-C3 over time. • To evaluate the effect of fazirsiran on changes in hepatic stiffness based on FibroScan® over time versus baseline (when available). • To evaluate effect of fazirsiran 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 fazirsiran treated patients.

- To determine the incidence and severity of treatment-emergent adverse events as a measure of the safety and tolerability of fazirsiran.
- To determine the incidence and titers of anti-drug antibodies (ADAs) to fazirsiran.

Exploratory Endpoints:

- To evaluate the effect of fazirsiran 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 fazirsiran (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 fazirsiran 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 fazirsiran 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).

Study Population/Subject Number: This study will be conducted in PiZZ patients with Alpha-1 Antitrypsin Deficiency. Both males and females are eligible, ages 18-75. In total, the study will consist of up to approximately 16 participants in three cohorts. Cohort 1 consists of 4 patients, Cohort 1b consists of 4 patients and Cohort 2 consists of 8 patients. Patients who complete any cohort may elect to participate in the treatment extension periods which would include an additional 12 doses as well as an optional repeat liver biopsy (performed following the fourth dose).

All eligible patients will require a pre-dose biopsy completed as part of the study within the screening window. Participants will consist of male and female adult PiZZ (based on genotype completed at Screening or from a source verifiable document) alpha-1 antitrypsin patients. Patients previously, currently, or never receiving AAT augmentation therapy are eligible for enrollment.

Number of Doses: Doses will be 100 or 200 mg of fazirsiran. A minimum of three 200 mg doses will be administered to patients in Cohort 1. Patients in Cohort 1b will receive a minimum of three 100 mg doses, and a minimum of five 200 mg doses will be administered to patients in Cohort 2. The maximum number of doses for patients completing the treatment

extension periods will be 15 doses for Cohort 1 and 1b patients and 17 doses for Cohort 2 patients.

Study Duration: For Cohort 1 and 1b, the duration of the study is approximately 36 weeks, from beginning of the Screening period to the phone call after the End-of-Study (EOS) visit. For Cohort 2, the duration of the study is approximately 60 weeks, from beginning of the Screening period to the phone call after the EOS visit. All patients will be invited to continue dosing with fazirsiran beyond the planned EOS visit as part of the treatment extension periods. As a participant in the treatment extensions, they will receive a total of twelve additional doses of fazirsiran at 12-week intervals. The expected total duration of the treatment extensions (Extension I, 12 months; and Extension II, up to 24 months) is up to 36 months (144 weeks), i.e., 3 years.

Study Visit Duration: For each participant, clinic visits for drug administration will last approximately up to 3 hours total, 2 hours pre-dose and 1-hour post-dose on dosing days. Shorter or longer visits on dosing days are acceptable and are per Investigator judgement. Clinic visits on non-dosing days are expected to last 1-2 hours.

Study Design/Methods: A multi-center, multi-dose, open-label, Phase 2 study will be conducted to evaluate the safety and efficacy of the investigational product, fazirsiran (TAK-999, 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 Institutional Review Board (IRB)/Ethics Committee (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 fazirsiran
- **Cohort 1b**: 100 mg dose of subcutaneous fazirsiran
- **Cohort 2**: 200 mg dose of subcutaneous fazirsiran

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 (SOA), 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.

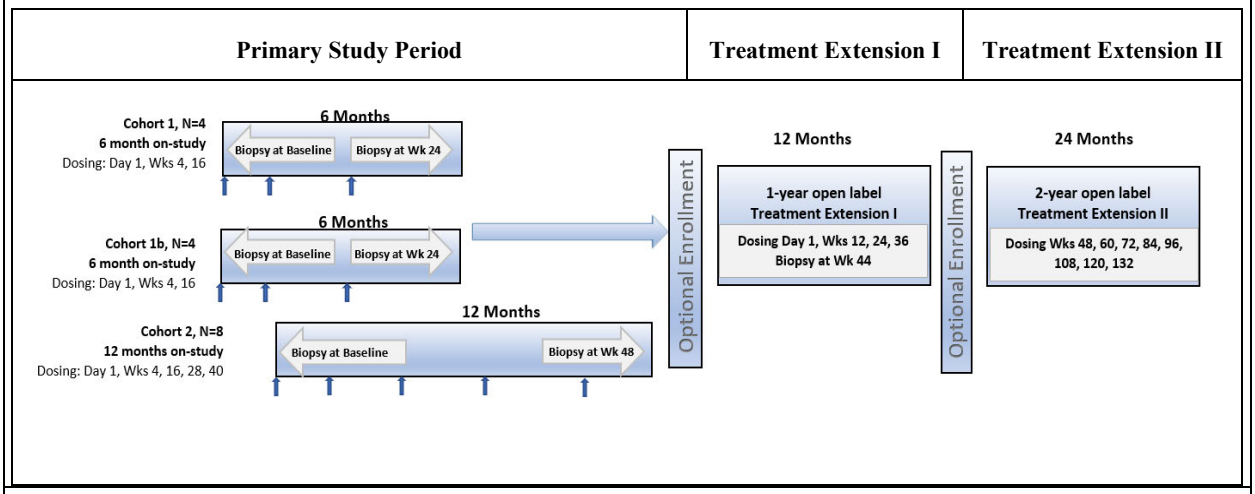
Treatment Extension I (12 Months)

Subjects who opt to continue in Treatment Extension I will receive the same dose level of fazirsiran as administered in their assigned initial cohort every 12 weeks (Q12W). Dosing with fazirsiran may continue approximately 12 weeks from the previous dose in the Primary Study Period. All subjects who opted to continue will have an optional 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 fazirsiran Q12W for up to an additional 24 months or until they roll over into another long-term Extension study, whichever comes first. Dosing with fazirsiran may continue approximately 12 weeks from the previous dose in Treatment Extension I. No biopsies will be collected in Treatment Extension II.

Study Schema



Subjects who proceed into Treatment Extension I and/or II will continue to receive the dose to which they were assigned at the start of the study. Based on cumulative safety, efficacy, and pharmacodynamics (PD) data from the fazirsiran clinical program (clinical studies AROAAT1001, AROAAT2001, and AROAAT2002), a fazirsiran dose (200 mg) was selected by the Sponsor. Following the respective country regulatory and ethics committees' approvals (including local approvals as necessary) of AROAAT2002 protocol amendment v7.0, all ongoing subjects will be consented and informed of the selected dose and subjects in Cohort 1b (100 mg) will begin receiving the selected dose at their next scheduled dosing timepoint.

Study Assessments:

Participants will undergo the following evaluations at regular intervals during the study (refer to SOA): medical history, physical examinations, vital sign measurements (blood pressure, temperature, heart rate, respiratory rate), weight, adverse events monitoring, electrocardiograms

(ECGs), urine pregnancy test/FSH (females), concurrent medication, pulmonary function testing (spirometry including vital capacity [VC], forced vital capacity [FVC], 1 second forced expiratory volume [FEV_1], FEV_1/VC, FEV_1/FVC, and diffusing capacity for carbon monoxide [DLCO]) and sample collection for hematology, coagulation, biochemistry, cardiac troponin, urinalysis, urine cotinine, anti-drug antibodies, drug screens, serum alpha-1 antitrypsin levels (where applicable), serum fibrosis biomarkers, liver biopsy, MRE (where feasible and available) and FibroScan® (where available).

Study visits will occur during the Screening window (Day -56 to -1), and as per the SOA. A telephone follow-up will occur 12 weeks (± 5 days) after the last dose to verify compliance with contraceptive measures and absence of any known pregnancy. Clinically significant changes including AEs will be followed until resolution is achieved, or until medically stable or the event is otherwise explained, or until the participant is lost to follow-up.

Baseline values will be those assessments obtained pre-dose within the closest proximity to the first dose of the study.

Histologic Assessments:

A liver biopsy will be collected at screening and at the end of the Primary Study Period (or at early termination). At the end of an additional 12 months of treatment for those subjects entering into and completing Treatment Extension I, an optional third liver biopsy may be collected based on each subject's consent. The biopsy will assess the following:

- Changes in AATD related histological metrics (e.g., steatosis, inflammation)
- Measure of size and number of PAS/D + globules (percent change and absolute change)
- Changes in Metavir fibrosis score

Additional PD assessments from the liver biopsy are listed under Other Pharmacodynamic Assessments.

Safety Assessments:

Safety assessments will be performed at specified time points per the SOA and will include the following:

- Vital signs: Resting heart rate, seated or semi-supine (same position each time is preferred) systolic/diastolic blood pressure, respiratory rate and temperature
- Clinical laboratory measurements (e.g., biochemistry, hematology, cardiac troponin, coagulation, urine cotinine and urinalysis)
- Resting ECG measurements (measured after participant is supine or semi-supine [same position each time is preferred] for at least 3 minutes)

- At each visit, participants will be asked about concomitant medications/therapy and will be instructed to volunteer any information regarding AEs and SAEs that they may have experienced. Any known untoward event that occurs beyond the AE reporting period that the Investigator(s) considers an SAE and possibly related to study treatment will be reported to Arrowhead.

- Injection site reactions (ISRs): Injection site reactions will be defined and graded as mild, moderate or severe based on clinical findings

- 90-day, post-last dose follow-up phone call to assess for pregnancy occurrence

- Physical examination (symptom directed as described in the SOA)

- Pulmonary Function Testing including spirometry (including VC, FVC, FEV_1) and DLCO

- Use of augmentation treatment at any time throughout the study and date when last augmentation was administered prior to each fazirsiran dose

- Time from baseline to initiation of augmentation therapy

- Number and severity of chronic obstructive pulmonary disease (COPD) exacerbations based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria will be evaluated as an AE of special interest

The AE reporting period for an enrolled participant will begin when the participant provides informed consent. Treatment-emergent AEs will be those defined as following dose administration, or in the event onset preceded dose administration, those AEs with severity or frequency increasing post-dose. All AEs that occur during the AE reporting period specified in the protocol must be reported, regardless of the relationship of the AE to study treatment. For this trial, the Investigator should evaluate the relatedness of an AE to investigational product using three categories: Not Related, Possibly Related and Probably Related. Laboratory abnormalities will be reported as an AE if considered clinically significant by the Investigator or if there are clinical sequelae. Any known SAE that occurs beyond the AE reporting period that the Investigator considers possibly or probably related to study treatment will be reported.

Other Pharmacodynamic Assessments:

The following PD measures and diagnostic studies will be collected for each dose and treatment group as per the SOA:

- Quantitative and/or % change in alpha-1 antitrypsin levels and mutant AAT protein (Z-AAT) levels

- Change in FibroScan® (where available)

- Change in magnetic resonance elastography (optional)
- Percent and absolute change in liver total (soluble plus insoluble) Z-AAT protein levels
- Percent and absolute change in liver Z-AAT soluble protein levels
- Percent and absolute change in liver Z-AAT insoluble protein levels
- Quantified and percent change in liver expression of liver fibrosis associated genes
- Percent and absolute change in SERPINA1 mRNA levels
- Measures of hepatic function including prothrombin time, partial thromboplastin time (PTT), international normalized ratio (INR), albumin, ALT, AST, gamma glutamyl transferase (GGT), platelet count, total bilirubin, and alkaline phosphatase
- Collagen content measurement (Masson's Trichrome, Sirius Red, morphometric analysis)
- Serum fibrosis biomarkers (e.g. PRO-C3)
- Calculated values indicative of liver disease (Fibrosis-4 index [FIB-4], aspartate aminotransferase-to-platelet ratio index [APRI])

Immunogenicity Assessments:

Emergence of anti-drug antibodies will be evaluated with serum samples collected as per the SOA.

Data Analysis:

Descriptive summaries will be presented for primary, secondary and exploratory endpoints using appropriate methods. A detailed statistical analysis plan (SAP) will be prepared and finalized prior to database lock.

Study Populations

- Safety Population: All patients who receive at least one dose of study drug. The Safety Population will be used for safety analyses.
- Full Analysis Set (FAS): All patients 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) population: All FAS patients who did not violate the protocol in a substantial manner, such determination to be made prior to database lock.

Sample Size

There were no formal sample size calculations made in this open-label exploratory study.

Screening, Tolerability and Safety Data:

In general, safety analyses will be performed, and the results summarized. Baseline safety assessments will be compared with measurements recorded post-baseline.

- Treatment-emergent AEs will be summarized using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and Preferred Term (PT), classified from verbatim terms.
- The incidence and frequency of AEs, SAEs, related AEs, related SAEs, and AEs leading to withdrawal, dose modification, or treatment discontinuation will be summarized by dose according to SOC and PT.
- AEs will also be summarized in listings. The duration of AEs will be determined and included in listings, along with the action taken and outcome.
- The incidence of laboratory abnormalities will be summarized.
- Vital sign measurements will be summarized at each scheduled time point using descriptive statistics.
- Physical examination findings will be summarized by time point and presented in participant listings.
- Clinically significant changes on ECG and changes in spirometry (including VC, FVC, FEV_1), and DLCO will be summarized.
- Pregnancy test/FSH results will be summarized separately by time point.
- 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 will be summarized using Kaplan Meier estimates.
- The percentage of patients experiencing an ISR (see definition of ISR in protocol) will be summarized using descriptive statistics.
- The number and percentage of patients with ADA positive by time will be summarized.

Treatment Stopping and Study Modification Rules:

A decision to stop the trial early or discontinue drug in an individual subject or group of patients **may** be indicated based on any of the following:

- In the case of two or more similar Serious Adverse Events both considered at least possibly related to fazirsiran, the trial will be put on halt even if the subject(s) is/are not discontinued from the study drug/study. The Principal Investigator and Sponsor will meet within 3 days of the Sponsor being notified of the 2nd event and within the timeframe of required regulatory agency notification. Available aggregated data will be reviewed to determine if the study remains safe to proceed, should be discontinued or should continue but with amendments. Restart of the trial will require approval of a substantial amendment from the competent authorities.

- Evaluation and fazirsiran discontinuation/dosing modification rules for elevated ALTs are provided in Appendix 1.

- Evaluation and fazirsiran study modification/discontinuation rules for declines in pulmonary function are provided in Appendix 2.

- Subject who becomes pregnant while in the study.

Sponsor or Investigator can discontinue any subject at any time. If such events (as described in #1, #2, or #3 above) occur and the subject is not discontinued from the study, the reason for not discontinuing the subject will be documented. Including, but not limited to the events listed above, the study may be paused to additional dosing to provide time to evaluate safety data and recommend the action to be taken, which may include, but is not limited to, one of the following:

- Discontinuation of a subject or group of patients from the study

- The study is stopped immediately with no further dosing

- The study will continue, but using a lower dose

- The study will continue as planned

  – Inclusion Criteria

To be eligible for enrollment, participants must meet all the following inclusion criteria:

- Male or non-nursing female patients 18-75 years of age, inclusive, at the time of Screening with previous diagnosis of PiZZ genotype Alpha-1 Antitrypsin Deficiency. PiZZ diagnosis from source verifiable medical records is permitted.

Otherwise, patients must undergo PiZZ confirmatory testing at Screening. PiMZ or PiSZ genotypes are not permitted.

- Able and willing to provide written informed consent prior to the performance of any study specific procedures.
- A 12-lead ECG at Screening that, in the opinion of the Investigator, has no abnormalities that compromise participant's safety in this study.
- Non-smoker (defined as does not smoke cigarettes daily for at least 12 months) with current non-smoking status confirmed by urine cotinine at screening and throughout the study. Patients may be on nicotine replacement (patch or gum). E-cigarettes (vapor) are not permitted. A positive urine cotinine result due to nicotine replacement is acceptable for enrollment at the discretion of the Investigator.
- Participants using highly effective contraception during the study and for 12 weeks following the last dose of fazirsiran. Males must not donate sperm for at least 12 weeks post last dose of study treatment. Females of childbearing potential must have a negative urine pregnancy test at Screening and on Day 1 pre-dose. Females not of childbearing potential must be post-menopausal (defined as cessation of regular menstrual periods for at least 12 months), confirmed by follicle-stimulating hormone (FSH) consistent with post-menopausal state based on lab reference ranges.
- Using twice the normal protection of birth control by using a condom AND one other form of either birth control pills (The Pill), depot or injectable birth control, IUD (Intrauterine Device), birth control patch (e.g., Ortho Evra), NuvaRing®, OR Surgical sterilization as a single form of birth control: i.e., tubal ligation, hysterectomy, bilateral oophorectomy, vasectomy or equivalently effective surgical form of birth control.
  - True subject abstinence for the duration of the study and 12 weeks after the dose of fazirsiran is acceptable only when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea methods are not considered "true" abstinence and are not acceptable methods of contraception.
- Participants who are willing and able to comply with all study assessments and adhere to the protocol schedule.
- Must have suitable venous access for blood sampling.

- No abnormal finding of clinical relevance at the Screening evaluation that in the opinion of the Investigator could adversely impact subject safety during the study or adversely impact study results.

- Liver biopsy indicating Metavir F1- F3 (or equivalent on other grading scales, see Appendix 3) liver fibrosis based on local pathologist read. All patients will require a liver biopsy during the screen period except for prior screened patients who now meet the fibrosis criteria as long as there is sufficient material for a baseline assessment as per specifications in the laboratory manual.

<u>All laboratory tests used as inclusion criteria may be repeated once and the repeat value may be used for inclusion purposes. Central labs will be utilized for the study, however local labs may be utilized as necessary due to emergent situations.</u>

– Exclusion Criteria

A potential participant will be excluded from the study if any of the following criteria apply:

- INR ≥1.5 at Screening. If based on opinion of Investigator and/or prescribing physician patient is appropriate for anticoagulant holiday, patient may stop taking anticoagulant for an appropriate washout period or reversal with vitamin K and if indicated a repeat INR within <1.5 would be acceptable. If INR is not indicated (direct thrombin inhibitors or Xa inhibitors) then appropriate washout period alone may be acceptable. (Note: Anti-platelet agents such as aspirin, clopidogrel or nonsteroidal anti-inflammatory drugs [NSAIDs] are acceptable but must be held 7 days before and 7 days after liver biopsy)

- ALT and AST levels >250 U/L at Screening (one retest permitted)

- Estimated glomerular filtration rate (eGFR) <60 ml/min at Screening (one retest permitted)

- Post-bronchodilation (if available) FEV_1 <65% of predicted at Screening in any subject **not** receiving AAT augmentation therapy.

- Post-bronchodilation (if available) FEV_1 <45% of predicted at Screening in any subject currently receiving AAT augmentation therapy on a regular basis and planning to continue AAT augmentation therapy for the duration of the study.

- Patients expected to have severe and unavoidable high-level exposure to inhaled pulmonary toxins during the study.

- Patients with recent (last 3 months) diagnosis of pneumonia are also excluded.

- Human immunodeficiency virus infection, as shown by the presence of anti-HIV antibody (sero-positive)
- Seropositive for HBV (HBsAg positive at Screening) or HCV (detectable HCV RNA at Screening). Cured HCV (positive antibody test without detectable HCV RNA is acceptable).
- Uncontrolled hypertension (systolic blood pressure [BP] >170 and diastolic BP >100 mmHg at Screening). Patients may rescreen once BP is successfully controlled.
- A history of torsades de pointes, ventricular rhythm disturbances (e.g., ventricular tachycardia or fibrillation), heart block (excluding first-degree block, being PR interval prolongation only), congenital long QT syndrome or new ST segment elevation or depression or new Q wave on ECG. Participants with a history of atrial arrhythmias should be discussed with the Medical Monitor
- Symptomatic heart failure (per New York Heart Association guidelines), unstable angina, myocardial infarction, severe cardiovascular disease (ejection fraction <20%, transient ischemic attack (TIA) or cerebrovascular accident (CVA) within 6 months prior to Screening
- History of malignancy within the last 1 year except for adequately treated basal cell carcinoma, squamous cell skin cancer, superficial bladder tumors, or in situ cervical cancer. Participants with other curatively treated malignancies who have no evidence of metastatic disease and >1-year disease-free interval may be entered following approval by the Medical Monitor.
- History of major surgery within the prior 1 month prior to Screening
- Regular use of alcohol within one month prior to the Screening visit (i.e., more than 14 units of alcohol per week [1 Unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol])
- Use of illicit drugs (such as cocaine, phencyclidine [PCP]) within 1 year prior to the Screening visit or positive urine drug screen at Screening (a urine drug screen positive for benzodiazepines, opioids or marijuana is acceptable for enrollment at the discretion of the Investigator if the positive test is due to a substance used for medical reasons).
- Use of an investigational agent or device within 30 days prior to dosing or current participation in an investigational study involving a therapeutic intervention. Patients receiving AAT augmentation therapy as part of a post-marketing study or other access program for approved therapies are acceptable.

- Blood donation (≥500 mL) within 7 days prior to study treatment administration.
- Any concomitant medical or psychiatric condition or social situation that would make it difficult to comply with protocol requirements or put the participant at additional safety risk. Patients with nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), metabolic syndrome, well controlled diabetes mellitus (even if on insulin) or hemochromatosis are acceptable if disease is stable and does not pose a significant threat to subject participation. Patients enrolled with NASH should have no plans to undergo bariatric surgery or initiate pharmaceutical therapy for NASH (such as Vitamin E or pioglitazone) during the course of the study. If already on such treatment, regimen must be stable for at least 12 weeks.
- A history of thromboembolic disease (including deep vein thrombosis or pulmonary embolism), myocardial infarction, stroke within six (6) months of screening.
- Participants who are unable to return for all scheduled study visits.
- Females of childbearing potential who are breastfeeding.
- Any other condition, that in the opinion of the Investigator would render the participant unsuitable for enrollment or could interfere with participating in and completing the study.
- Previous diagnosis of decompensated liver cirrhosis or complications of cirrhosis (e.g., varices, ascites, hepatic encephalopathy) based on source verifiable medical record.
- Diagnosis of F4 (Metavir) or similar grading scale equivalent indicating definitive cirrhosis on pre-dose liver biopsy completed as part of the AROAAT2002 study based on local pathologist read or based on historical liver biopsy (last 6 months from consent) with a source verifiable pathologist read of definitive liver cirrhosis.

Note: Sponsor Medical Monitor has the option to exclude the enrollment of a participant if, based upon the participant's medical history or Screening results, it is felt that a participant's safety may be at risk.

All laboratory tests used as exclusion criteria may be repeated once and the repeat value may be used for exclusion purposes. Central labs will be utilized for the study, however local labs may be utilized as necessary due to emergent situations.

Table 1: Cohort 1 & 1b Schedule of Assessments

Assessment visit	Baseline / Screen[1]		Day 1 Dosing day	24-48 hr post-dose	Wk 2	Wk 4 Dosing day	24-48 hr post-dose	Wk 6	Wk 16 Dosing day	24-48 hr post-dose	Wk 24 visit	12 Wks post last dose	Early Term
Window in days	-56 to Day -1				± 5	± 5		± 5	± 14		± 14		
Informed Consent	X												
Eligibility Criteria	X												
Demographics/Medical History	X												
BMI	X												
Weight (Optional)	X		X						X		X		X
Urine Cotinine	X							X			X		X
Urine Drug Screen	X												
Hepatitis/HIV	X												
FSH in post-menopausal females	X												
Pulmonary Function Testing[2]	X		X			X			X		X[10]		X[10]
FibroScan®	X										X[10]		X[10]
Magnetic Resonance Elastography (Optional)	X[11]										X		X
Liver Biopsy	X										X[10]		X[10]
PiZZ Genotype	X[3]												
Physical Exam	X		X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X		X
Urine Pregnancy Test	X		X[5]			X[5]			X[5]		X		X
ECG	X		X[6]			X[6]			X[6]		X		X
Vital Signs (BP, temp, heart rate, respiratory rate)	X		X[7]	X	X	X[7]	X	X	X[7]	X	X		X
Clinical Labs (chem, heme, coag, UA)	X[8]		X[8]	X	X	X[8]	X	X	X[8]	X	X[8]		X[8]

ENROLLMENT

Table 1: Cohort 1 & 1b Schedule of Assessments (Continued)

Assessment visit	Baseline / Screen[1]	ENROLLMENT	Day 1 Dosing day	24-48 hr post-dose	Wk 2	Wk 4 Dosing day	24-48 hr post-dose	Wk 6	Wk 16 Dosing day	24-48 hr post-dose	Wk 24 visit	12 Wks post last dose	Early Term
Window in days	-56 to Day -1				± 5	± 5		± 5	± 14		± 14		
Alpha-1 Antitrypsin Level	X		X[9]		X	X[9]		X	X[9]		X		X
PRO-C3			X[9]			X[9]			X[9]		X		X
Anti-drug Antibodies			X[9]					X			X		X
Concomitant Meds/Therapies	X		X	X	X	X	X	X	X	X	X		X
Adverse Events	X		X	X	X	X	X	X	X	X	X		X
Fazirsiran Administration			X			X			X				
Pregnancy Follow Up												X	
Calculate FIB-4, APRI	X		X			X			X		X		X

1. Screen visit may be split into separate days per site discretion.
2. Pulmonary function testing includes VC, FVC, FEV_1, FEV_1/VC, FEV_1/FVC, and DLCO. Pertinent study FEV_1 will be based on post-bronchodilation value. If FEV_1 at screen does not meet inclusion/exclusion, there is no need to perform DLCO.
3. Only if genotype not already confirmed and documented in medical record.
4. Symptom-directed PEs to be performed by visit as necessary.
5. Negative urine pregnancy test must be confirmed pre-dose on dosing days in pre-menopausal females.
6. On dosing days, ECGs will be performed at pre-dose, and post dose only if clinically warranted based on reported AEs. A clinically significant abnormal result will be repeated in triplicate.
7. On dosing days vital sign assessment will be performed pre-dose, and 1-hour post-dose; more frequently per hour if necessary.
8. Participants should be fasting (water only) for a minimum of two hours prior to the collection of the clinical labs.
9. On dosing days, samples will be drawn pre-dose.
10. Evaluations of VC, FVC, FEV_1, DLCO, liver biopsy and FibroScan® should be completed in the following order: VC, FVC, FEV_1 and DLCO on same day, then FibroScan® prior to liver biopsy. FibroScan should not occur after liver biopsy.

11. Magnetic resonance elastography performed at the screen/baseline visit and/or prior to this visit, but within the screening period (Day -56 to Day -1), should be collected at the screen/baseline visit and/or retrospectively (if applicable) for analysis.

A visit specified as Week X has a target date of Day 1+X number of weeks, for example, the Week 4 visit ideally occurs 28 days after Day 1 (on Day 29). In Treatment Extension I, the calendar resets and Day 1 will be the first dose received during the treatment extension periods (approximately 12 weeks after the last dose in either Cohort 1, 1b, or 2) although the subject may have received previous doses while participating in Cohort 1, 1b, or 2.

Table 2: Cohort 2 Schedule of Assessments

Assessment visit	Baseline / Screen[1]	ENROLLMENT	Day 1 Dosing day	24-48 hr post-dose	Wk 2	Wk 4 Dosing day	24-48 hr post-dose	Wk 6	Wk 16 Dosing day	24-48 hr post-dose	Wk 22	Wk 28 Dosing day	Wk 34	Wk 40 Dosing day	Wk 48 visit	12 Wks post last dose	Early Term
Window in days	-56 to Day -1				± 5	± 5		± 5	± 14		± 14	± 14	± 14	± 14	± 14		
Informed Consent	X																
Eligibility Criteria	X																
Demographics/Medical History	X																
BMI	X																
Weight (Optional)	X		X						X		X		X		X		X
Urine Cotinine	X							X			X		X		X		X
Urine Drug Screen	X																
Hepatitis/HIV	X																
FSH in post-menopausal females	X																
Pulmonary Function Testing[2]	X		X			X			X			X		X	X[10]		X
FibroScan®	X														X[10]		X
Magnetic Resonance Elastography (Optional)	X[11]														X		X
Liver Biopsy	X														X[10]		X
PiZZ Genotype	X[3]																

Table 2: Cohort 2 Schedule of Assessments (Continued)

Assessment visit	Baseline / Screen[1]	ENROLLMENT	Day 1 Dosing day	24-48 hr post-dose	Wk 2	Wk 4 Dosing day	24-48 hr post-dose	Wk 6	Wk 16 Dosing day	24-48 hr post-dose	Wk 22	Wk 28 Dosing day	Wk 34	Wk 40 Dosing day	Wk 48 visit	12 Wks post last dose	Early Term
Window in days	-56 to Day -1				± 5	± 5		± 5	± 14		± 14	± 14	± 14	± 14	± 14		
Physical Exam	X		X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X		X
Urine Pregnancy Test	X		X[5]			X[5]			X[5]			X[5]		X[5]	X		X
ECG	X		X[6]			X[6]			X[6]			X[6]		X[6]	X		X
Vital Signs (BP, temp, heart rate, respiratory rate)	X		X[7]	X	X	X[7]	X	X	X[7]	X	X	X[7]	X	X[7]	X		X
Clinical Labs (chem, heme, coag, UA)	X[8]		X[8]	X	X	X[8]	X	X	X[8]	X	X	X[8]	X	X[8]	X[8]		X
Alpha-1 Antitrypsin Level	X		X[9]		X	X[9]		X	X[9]		X	X[9]	X	X[9]	X		X
PRO-C3			X[9]			X[9]			X[9]			X[9]		X[9]	X		X
Anti-drug Antibodies			X[9]					X							X		X
Concomitant Meds/Therapies	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse Events	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Fazirsiran Administration			X			X			X			X		X			
Pregnancy Follow Up																X	
Calculate FIB-4, APRI	X		X			X			X			X		X	X		X

1. Screen visit may be split into separate days per site discretion.
2. Pulmonary function testing includes VC, FVC, FEV_1, FEV_1/VC, FEV_1/FVC, and DLCO. Pertinent study FEV_1 will be based on post-bronchodilation value. If FEV_1 at screen does not meet inclusion/exclusion, there is no need to perform DLCO.
3. Only if genotype not already confirmed and documented in medical record.
4. Symptom-directed PEs to be performed by visit as necessary.
5. Negative urine pregnancy test must be confirmed pre-dose on dosing days in pre-menopausal females.
6. On dosing days, ECGs will be performed at pre-dose, and post dose only if clinically warranted based on reported AEs. A clinically significant abnormal result will be repeated in triplicate.
7. On dosing days vital sign assessment will be performed pre-dose, and 1-hour post-dose; more frequently per hour if necessary.
8. Participants should be fasting (water only) for a minimum of two hours prior to the collection of the clinical labs.
9. On dosing days, samples will be drawn pre-dose.
10. Evaluations of VC, FVC, FEV_1, DLCO, liver biopsy and FibroScan® should be completed in the following order: VC, FVC, FEV_1 and DLCO on same day, then FibroScan® prior to liver biopsy. FibroScan should not occur after liver biopsy.
11. Magnetic resonance elastography performed at the screen/baseline visit and/or prior to this visit, but within the screening period (Day -56 to Day -1), should be collected at the screen/baseline visit and/or retrospectively (if applicable) for analysis.

A visit specified as Week X has a target date of Day 1+X number of weeks, for example, the Week 4 visit ideally occurs 28 days after Day 1 (on Day 29). In Treatment Extension I, the calendar resets and Day 1 will be the first dose received during the treatment extension periods (approximately 12 weeks after the last dose in either Cohort 1, 1b, or 2) although the subject may have received previous doses while participating in Cohort 1, 1b, or 2.

Table 3: Treatment Extension I Schedule of Assessments

Assessment visit		**Day 1 Dosing day (12 weeks after last dose in Cohort 1, 1b, or 2)**	**Wk 6**	**Wk 12 Dosing day**	**Wk 18**	**Wk 24 Dosing day**	**Wk 30**	**Wk 36 Dosing day**	**Wk 44 Biopsy visit**	**Early Term**
Window in days		**± 14**	**± 14**	**± 5**	**± 14**	**± 5**	**± 14**	**± 5**	**± 14**	
Fazirsiran Administration	TREATMENT EXTENSION I	X		X		X		X		
Pulmonary Function Testing[1]		X		X		X		X	X[8]	X
FibroScan®									X[8]	X
Magnetic Resonance Elastography (Optional)									X	X
Liver Biopsy (Optional)									X[8]	X
Physical Exam		X		X[2]		X[2]		X[2]	X	X
Urine Pregnancy Test		X[3]		X[3]		X[3]		X[3]	X	X
ECG		X[4]		X[4]		X[4]		X[4]	X	X
Vital Signs (BP, temp, heart rate, respiratory rate)		X[5]		X[5]		X[5]		X[5]	X	X
Urine Cotinine									X	X
Clinical Labs (chem, heme, coag, UA)		X[6]		X[6]		X[6]		X[6]	X	X
Alpha-1 Antitrypsin Level		X[7]		X[7]		X[7]		X[7]	X	
PRO-C3		X[7]		X[7]		X[7]		X[7]	X	X
Anti-drug Antibodies						X[7]			X	X
Concomitant Meds/Therapies		X		X		X		X	X	X
Adverse Events		X		X		X		X	X	X
Calculate FIB-4, APRI		X		X		X		X	X	X
Weight (optional)				X		X		X	X	X
Telephone Contact to Evaluate for AEs			X		X		X			

1. Pulmonary function testing includes VC, FVC, FEV_1, FEV_1/VC, FEV_1/FVC, and DLCO. Pertinent study FEV_1 will be based on post-bronchodilation value.
2. Symptom-directed PEs to be performed by visit as necessary.

3. Negative urine pregnancy test must be confirmed pre-dose on dosing days in pre-menopausal females.
4. On dosing days, ECGs will be performed at pre-dose, and post dose only if clinically warranted based on reported AEs. A clinically significant abnormal result will be repeated in triplicate.
5. On dosing days vital sign assessment will be performed pre-dose, and 1-hour post-dose; more frequently per hour if necessary.
6. Participants should be fasting (water only) for a minimum of two hours prior to the collection of the clinical labs.
7. On dosing days, samples will be drawn pre-dose.
8. Evaluations of VC, FVC, FEV_1, DLCO, optional liver biopsy and FibroScan® should be completed in the following order: VC, FVC, FEV_1 and DLCO on same day, then FibroScan® prior to optional liver biopsy. FibroScan should not occur after optional liver biopsy.

A visit specified as Week X has a target date of Day 1+X number of weeks, for example, the Week 4 visit ideally occurs 28 days after Day 1 (on Day 29). In Treatment Extension I, the calendar resets and Day 1 will be the first dose received during the treatment extension periods (approximately 12 weeks after the last dose in either Cohort 1, 1b, or 2) although the subject may have received previous doses while participating in Cohort 1, 1b, or 2.

Table 4: Treatment Extension II Schedule of Assessments

Assessment visit		**Wk 48 Dosing day (12 weeks after last dose in Treatment Extension I)**	**Wk 54**	**Wk 60 Dosing day**	**Wk 66**	**Wk 72 Dosing day**	**Wk 78**	**Wk 84 Dosing day**	**Wk 90**	**Wk 96 Dosing day**	**Wk 102**	**Wk 108 Dosing day**	**Wk 114**	**Wk 120 Dosing day**	**Wk 126**	**Wk 132 Dosing day**	**Wk 140 EOS visit**	**12 Wks post last dose**	**Early Term**
Window in days		± 5	± 14	± 5	± 14	± 5	± 14	± 5	± 14	± 5	± 14	± 5	± 14	± 5	± 14	± 5	± 14	± 14	
Fazirsiran Administration	**TREATMENT EXTENSION II**	X		X		X		X		X		X		X		X			
Pulmonary Function Testing[1]		X		X		X		X		X		X		X		X	X		X
FibroScan®																	X		X
Magnetic Resonance Elastography (Optional)																	X		X
Physical Exam		X		X[2]		X[2]		X[2]		X[2]		X[2]		X[2]		X[2]	X		X
Urine Pregnancy Test		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]	X		X
ECG		X[4]		X[4]		X[4]		X[4]		X[4]		X[4]		X[4]		X[4]	X		X
Vital Signs (BP, temp, heart rate, respiratory rate)		X[5]		X[5]		X[5]		X[5]		X[5]		X[5]		X[5]		X[5]	X		X
Urine Cotinine																	X		X
Clinical Labs (chem, heme, coag, UA)		X[6]		X[6]		X[6]		X[6]		X[6]		X[6]		X[6]		X[6]	X		X
Alpha-1 Antitrypsin Level		X[7]		X[7]		X[7]		X[7]		X[7]		X[7]		X[7]		X[7]	X		
PRO-C3		X[7]		X[7]		X[7]		X[7]		X[7]		X[7]		X[7]		X[7]	X		X
Concomitant Meds/Therapies		X		X		X		X		X		X		X		X	X		X
Adverse Events		X		X		X		X		X		X		X		X	X		X

Pregnancy Follow Up																	X	
Calculate FIB-4, APRI		X		X		X		X		X		X		X		X	X		X
Weight (optional)				X		X		X		X		X		X		X	X		X
Telephone Contact to Evaluate for AEs			X		X		X		X		X		X		X				

1. Pulmonary function testing includes VC, FVC, FEV_1, FEV_1/VC, FEV_1/FVC, and DLCO. Pertinent study FEV_1 will be based on post-bronchodilation value.
2. Symptom-directed PEs to be performed by visit as necessary.
3. Negative urine pregnancy test must be confirmed pre-dose on dosing days in pre-menopausal females.
4. On dosing days, ECGs will be performed at pre-dose, and post dose only if clinically warranted based on reported AEs. A clinically significant abnormal result will be repeated in triplicate.
5. On dosing days vital sign assessment will be performed pre-dose, and 1-hour post-dose; more frequently per hour if necessary.
6. Participants should be fasting (water only) for a minimum of two hours prior to the collection of the clinical labs.
7. On dosing days, samples will be drawn pre-dose.

A visit specified as Week X has a target date of Day 1+X number of weeks, for example, the Week 4 visit ideally occurs 28 days after Day 1 (on Day 29).

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2. STUDY INFORMATION AND SIGNATURES

Investigator's Statement:

I have read and understood the information in this protocol and agree to conduct the trial according to the protocol (subject to any amendments) and in accordance with the principles of Good Clinical Practice. I have read and agree to comply with the Investigator obligations stated in this protocol. Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of participants.

I agree to conduct in person or to supervise the trial.

I agree to ensure that all that assist me in the conduct of the study are aware of their obligations.

Principal Investigator:

_____ _____

Signature Date

_____

Printed Name

3. LIST OF ABBREVIATIONS AND TERMS

AAT	Alpha-1 antitrypsin
AATD	Alpha-1 antitrypsin deficiency
ADA	Anti-drug antibodies
ADS-001	Drug substance (API, lyophilized powder) containing RNAi trigger (also referred to as fazirsiran, ARO-AAT, or TAK-999)
AE	Adverse event
ALT	Alanine aminotransferase
API	Active Pharmaceutical Ingredient
APRI	Aspartate aminotransferase-to-platelet ratio index
ARO	Arrowhead Pharmaceuticals, Inc
ARO-AAT	Short name for ARO-AAT Injection
ARO-AAT Injection	Clinical drug product solution ready for SC injection (also referred to as Fazirsiran Injection or TAK-999 Injection)
AST	Aspartate transaminase
ATS-ERS	American Thoracic Society and European Respiratory Society
BMI	Body mass index
BP	Blood pressure
cGCP	Current Good Clinical Practice
cGMP	Current Good Manufacturing Practice
COPD	Chronic obstructive pulmonary disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically significant
CTN	Clinical Trial Notification
CV	Coefficient of variation
CVA	Cerebrovascular accident

DLCO	Diffusing capacity for carbon monoxide
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EOS	End of Study
FAS	Full Analysis Set
Fazirsiran	Drug substance (API, lyophilized powder) containing RNAi trigger (also referred to as ADS-001, ARO-AAT, or TAK-999)
Fazirsiran Injection	Clinical drug product solution ready for subcutaneous injection (also referred to as ARO-AAT Injection or TAK-999 Injection)
FDA	Food and Drug Administration
FEV_1	1 second forced expiratory volume
FIB-4	Fibrosis-4 index
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation
INR	International normalized ratio
IRB	Institutional Review Board
ISR	Injection site reaction

IUD	Intrauterine device
LD	Lactate dehydrogenase
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean cell volume
mmHg	Millimeters of mercury
MRE	Magnetic resonance elastography
mRNA	Messenger RNA
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NHP	Non-human primate
NOAEL	No observed adverse effect level
NSAID	Nonsteroidal anti-inflammatory drug
PD	Pharmacodynamic
PI	Principal Investigator
PiZZ	Homozygous Z allele individuals
PP	Per Protocol
PK	Pharmacokinetic
PT	Preferred term
PTT	Partial thromboplastin time
Q4W	Once every four weeks
Q12W	Once every twelve weeks
QT	QT interval - a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
RBC	Red blood cell
RNAi	RNA interference

SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
siRNA	Short interfering RNA oligonucleotides
SOA	Schedule of Assessments
SOC	System Organ Class
TIA	Transient ischemic attack
ULN	Upper limit of normal
VC	Vital capacity
Z-AAT	Mutant AAT protein from Z allele

4. INTRODUCTION

4.1. Background Information

Alpha-1 antitrypsin deficiency is an autosomal co-dominant genetic disorder with a prevalence range of 1/1500-1/5000 that causes early pulmonary disease in adults and liver disease in children and adults (Nelson et al., 2012). Alpha-1-antitrypsin (AAT) is a 52 kDa circulating glycoprotein protease inhibitor of the serpin family. The primary function of AAT is to inhibit neutrophil elastase to prevent excessive elastase-induced tissue damage. Normally, AAT is synthesized primarily in hepatocytes and several grams daily are secreted directly into the serum. In lung parenchyma, AAT is critical for protection of alveolar interstitial elastin from degradation by neutrophil elastase. A lack of adequate levels of functional AAT leads to damage of lung elastin by neutrophil elastase and the development of early emphysema. It generally takes decades for lung disease to manifest and usually requires additional environmental insult, usually cigarette smoking. Low plasma AAT levels that lead to pulmonary disease in individuals homozygous for the Z mutation (PiZZ) are not from a lack of synthesis (except in null/null patients) but from a disruption of its processing and secretion by hepatocytes. AAT is normally secreted in monomeric form, but the mutant AAT protein (Z-AAT) synthesized by PiZZ individuals contains a single point mutation that results in low secretion, accumulation and polymer formation in hepatocytes leading to liver disease. Lung disease is frequently treated with AAT replacement therapy, and fewer than 10,000 patients are on replacement or "augmentation" therapy in the U.S. (Stoller et al., 2012). However, augmentation therapy does nothing to treat liver disease, and no specific therapy is available for alpha-1 antitrypsin deficiency (AATD)-associated liver disease.

In clinical practice, over 90% of AAT deficiency is due to the PiZZ genotype (DeSerres et al., 2012). PiZZ adult patients may initially present with clinical signs of pulmonary disease such as dyspnea, cough, chronic bronchitis, or they may initially present with signs of liver disease such as elevated transaminases or bilirubin, hepatitis, or cirrhosis (American Thoracic Society/European Respiratory Society 2003). Pediatric patients typically present with clinical symptoms of liver disease, which may include asymptomatic chronic hepatitis, failure to thrive, poor feeding or hepatomegaly and splenomegaly. However, disease natural history in both pediatric and adult patients is variable.

A 2018 publication by Clark et al., examined 94 PiZZ adults using liver biopsy and various other noninvasive measures of liver disease (e.g., transient elastography, Fibrosis-4 index [FIB-4]) (Clark et al., 2018). In this cohort, the prevalence of clinically significant liver disease (≥F2) was 35.1%. The presence of accumulated Z-AAT globules, portal inflammation, and hepatocellular degeneration were associated with clinically significant fibrosis. Similarly, accumulation of Z-AAT globules, portal inflammation, and hepatocellular degeneration are seen on histologic evaluation of the PiZ mouse model liver.

4.2. Development and Mechanism of Action of Fazirsiran

Since Z-AAT protein accumulation is the underlying cause of hepatocyte injury in AATD, preventing monomer accumulation and polymer formation is a logical step for treating AATD-associated liver disease. This is supported by the lack of liver disease in AATD patients with null/null genotypes. These rare patients completely lack AAT synthesis. They present clinically with pulmonary disease, but since they have no hepatocyte production or accumulation of mutant AAT protein, they are devoid of liver disease.

One mechanism of preventing Z-AAT accumulation is through RNA interference (RNAi)-mediated gene silencing of Z-AAT protein production. RNA interference (RNAi)-based therapeutics have the potential to silence the expression of any disease gene. RNAi is a naturally occurring process by which short interfering RNA oligonucleotides (siRNAs) trigger a sequence-specific down-modulation of gene expression. By delivering siRNAs targeting AAT sequences to the liver, it is possible to knock down expression of AAT messenger RNAs (mRNAs) in hepatocytes. This reduces the synthesis of Z-AAT proteins that are responsible for hepatic disease in AATD. Reductions in levels of Z-AAT protein production should allow for degradation or secretion of Z-AAT proteins already present, prevent further hepatocyte injury, reduce inflammation and fibrosis and allow for hepatic healing. Knocking down Z-AAT protein production with resulting reduction of both mutant protein globules and fibrosis in the PiZZ transgenic mouse has been well demonstrated by Teckman et al., 2013 (Teckman et al., 2013). Based on findings in mouse models of AATD-associated liver disease and effective treatment of other hepatic diseases such as viral hepatitis, it is also expected that with effective reduction in necro-inflammation, fibrosis and early cirrhosis should reverse, as well, with effective, chronic treatment.

Arrowhead Pharmaceuticals, Inc. has developed a drug candidate, fazirsiran (TAK-999, also referred to as ARO-AAT) to treat AATD-associated liver disease through an RNAi-mediated mechanism. Fazirsiran is a novel hepatocyte targeted RNAi trigger molecule which is conjugated to N-acetyl-galactosamine to facilitate hepatocyte endocytosis. Fazirsiran is highly effective at knocking down the AAT mRNA gene transcript and reducing the production of hepatic Z-AAT protein.

4.3. Fazirsiran Pre-Clinical Pharmacology and Studies

Preclinical pharmacology of fazirsiran was evaluated in the PiZ transgenic mouse model of AATD liver disease and in cynomolgus monkeys. In the mouse model, treatment with fazirsiran resulted in dramatically reduced serum Z-hAAT protein levels, which correlated with reduced liver Z-hAAT mRNA levels. Multi-dose studies showed that mice treated with fazirsiran have less Z-hAAT monomer and a reduced burden of Z-hAAT polymer in the liver compared to saline-treated mice. As expected, these mice also showed reductions in hepatocyte necrosis, liver inflammation and down-regulation of fibrosis-related genes. Importantly, hepatocyte necrosis and liver inflammation are also seen on histologic evaluation of human PiZZ patient livers. Fazirsiran treatment in cynomolgus monkeys resulted in a maximum reduction in circulating AAT of approximately 93% with 80% or greater knockdown sustained for more than 8 weeks

after receiving two once every four weeks (Q4W) 3 mg/kg doses of fazirsiran. Further information on the pre-clinical pharmacology studies is provided in the Investigator's Brochure.

4.4. Fazirsiran Pre-Clinical Pharmacokinetic and Product Metabolism Studies

Pharmacokinetic (PK) parameters for fazirsiran have been evaluated in both rats and monkeys. Results of these studies can be found in the Investigator's Brochure.

4.5. Fazirsiran Pre-Clinical Toxicology Studies

Fazirsiran has been clinically well tolerated in rats and in non-human primate (NHP) toxicology studies. Details regarding Good Laboratory Practice (GLP) and non-GLP toxicology results are provided in the Investigator's Brochure.

4.6. Fazirsiran Clinical Pharmacology, Pharmacokinetic and Clinical Safety

Fazirsiran has been evaluated in the AROAAT1001 study which investigated the safety and pharmacodynamic (PD) effects of single and multiple doses of fazirsiran in a healthy volunteer population. Full results of the completed AROAAT1001 study, interim results of the ongoing AROAAT2002, and preliminary (blinded safety data) from the ongoing AROAAT2001 study are available in the Investigator's Brochure.

4.7. Rationale for the Study

This study is intended to explore differences in histological and PD responses with different durations of treatment (e.g., biopsy at approximately 6, 12, 18 and 24 months post-dose) versus pre-dose baseline. This will inform on duration of treatment required to show therapeutic effect.

Intracellular mutant (Z-AAT) misfolded protein accumulation is the underlying cause of hepatocyte injury in AATD (Torres-Durán et al., 2018). Preventing hepatic accumulation of misfolded protein by silencing Z-AAT synthesis is a logical intervention for treating AATD-associated liver disease. This is supported by the development of liver tumors and upregulating of fibrosis associated genes in the PiZ transgenic mouse model and by the lack of liver disease in AATD patients with null/null genotypes versus the presence of liver disease in PiZZ genotype patients (Feldman et al., 1975). Treatment of patients with fazirsiran is expected to reduce hepatic production of AAT, leading to reductions in intra-hepatic misfolded monomer, polymer and reduction in AAT serum levels. Data obtained from nonclinical pharmacology studies in the PiZ mouse model have demonstrated that multiple doses of fazirsiran administered every other week for 4 doses can prevent the accumulation of, and even reduce the burden of already present Z-hAAT protein in the livers of PiZ mice (Wooddell et al., 2020). Based on this animal data, it is expected that multi-dose treatment with fazirsiran in AATD patients will prevent further accumulation of intra-hepatic mutant protein while allowing endogenous clearance mechanisms to remove Z-AAT protein already accumulated. This removal of the offending agent should

reduce/eliminate necro-inflammation, which should prevent further liver injury while allowing fibrosis due to earlier injury to remodel. The ability of the liver to heal with removal of an inciting insult has been demonstrated with treatment of other causes of liver injury including hepatitis B virus (HBV), hepatitis C virus (HCV) and nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) (Ellis et al., 2012).

The AROAAT2002 design and conduct is supported by existing nonclinical pharmacology and toxicology data as well as data from a Phase 1 clinical study AROAAT1001 in healthy volunteers which evaluated safety, PK, and PD effect of single and multiple escalating doses of fazirsiran. AATD patients with AATD associated liver disease will require multiple doses of fazirsiran to sustain hepatic silencing of AAT production. This study will assess effects after three doses of fazirsiran compared with five doses, with each dose after the second dose administered approximately every 12 weeks. Dose levels of 100 mg or 200 mg were planned in this study based on PD results seen at these dose levels in the AROAAT1001 study which supports PD effect and high potential for Z-AAT silencing at both dose levels. Single dose PD effect from the AROAAT1001 study indicates that AAT serum protein levels generally reach nadir, but not always full suppression to below lower limit of quantitation around Week 6 to 8 and start to rebound by approximately Week 12 after a single dose. This observed time until rebound supports quarterly dosing. This study also demonstrated that a second dose at Day 29 (4 weeks after initial dose) resulted in complete suppression of circulating AAT levels that was sustained. (See Investigator's Brochure for details.) Based on these results, it was determined that 2 doses administered 28 days apart would quickly lead to maximal and sustained reduction in hepatic AAT production but thereafter dosing could be quarterly. Hence, this was viewed as the best approach to achieve the fullest level of hepatic reduction of the insulting agent while minimizing overall patient exposure by moving to quarterly dosing.

Based on non-clinical studies in the PiZ mouse model and experience with liver recovery from other necro-inflammatory diseases such as viral hepatitis, it is highly likely that dose administration beyond a single dose will be required to reduce liver polymer sufficiently to reduce globule levels, necro-inflammation and hopefully allow repair of hepatic architecture. Based on other precedents as discussed above, improvement of fibrosis or other adverse liver histologic findings due to AATD liver disease may require long term therapy to show improvement. Two cohorts of differing treatment durations will assess the time until liver histological improvements may be observed.

The current study uses liver biopsy to obtain tissue samples for the histological measurement of drug effect at the end of the study. Non-invasive measures (including FibroScan®) of PD effect are also included. However, liver biopsy remains the gold standard for histological evaluation in clinical studies.

4.8. Risk Assessment for Participants

- **Liver Biopsy Risk:** Performance of liver biopsies is commonly part of the standard of care in patients with liver disease related to AATD as well as other adult liver diseases. While it is a common procedure, like any procedure it is associated with

some risk. The risk of bleeding associated with biopsies requiring blood transfusion or hospitalization is 0.04% or less and the risk of less severe but clinically significant events (causing pain, tachycardia or lower blood pressure) is estimated at 0.2% (Rockey et al., 2009). Several larger studies show that complications and serious bleeding related to liver biopsy are overwhelmingly more likely in patients with serious clotting disorders, malignancy, and other serious health conditions that are described in the exclusion criteria for this study. Measures of hemostatic function (e.g., platelets, international normalized ratio [INR]) will be conducted prior to biopsy, and may be used to exclude any participant at increased risk for procedural complications. Thrombocytopenia and elevated INR are exclusionary for this study. Therefore, the risk of liver biopsy related complications in this study is acceptable and similar to other studies using liver histology as an endpoint. Monitoring and recovery of the patient following the procedure will be consistent with locally accepted standards of clinical practice.

- **Pulmonary Risk**: AATD may manifest as pulmonary disease in adult patients. AATD pulmonary disease is often treated with AAT augmentation therapy in countries where this therapy has been approved and is available. Fazirsiran is intended to reduce hepatic production of AAT and will, by extension, reduce serum levels of AAT protein. In AATD patients, this protein is poorly functional in its capacity to inhibit neutrophil elastase relative to wild type protein. Pulmonary disease in AATD requires decades to develop, especially in the absence of smoking, and it is extremely unlikely that short-term reduction in serum AAT will worsen pulmonary disease, particularly in non-smokers. Sponsor anticipates an approximate 90% reduction of serum Z-AAT to represent near maximum reduction possible with a hepatocyte targeted RNAi mechanism based on previous experience. Extra-hepatic production, including locally in the lung, is not expected to be reduced by fazirsiran.

  Based on the lack of a statistically significant difference between active and placebo adverse changes in pulmonary function metrics seen in the AROAAT1001 study using siRNA to transiently reduce serum AAT levels, and the fact that pulmonary disease in PiZZ patients with very low and already dysfunctional serum AAT takes decades to develop (if it develops at all), we do not believe that transient lower AAT serum levels represents a significant pulmonary risk to AATD patients, many of whom may already have lung disease and who may be on AAT augmentation therapy. This is also the opinion of key pulmonology opinion leaders who manage AATD patients. Steps will be taken in this study to mitigate this theoretical risk.

  - Patients who smoke or with a significant smoking history will be excluded from this study, at least initially, and their non-smoking status will be confirmed by measuring urinary cotinine at Screening and throughout the study.

  - Patients expected to have severe and unavoidable exposure to inhaled environmental exposure during the study will be excluded.

- Above standard of care pulmonary monitoring is implemented during the study with vital capacity (VC), forced vital capacity (FVC), 1 second forced expiratory volume (FEV_1), FEV_1/FVC, FEV_1/VC, and diffusing capacity for carbon monoxide (DLCO) measured pre-dose and at every dosing visit.

- Patients without sufficient pulmonary reserve at baseline (e.g., post-bronchodilation FEV_1 <65 % of predicted) are excluded unless using AAT augmentation therapy. Patients with recent lower respiratory infections (such as pneumonia) are also excluded.

- Standard of care emphysema treatment (e.g., corticosteroids, bronchodilators) is permitted.

- Any patient developing pulmonary symptoms or worsening pulmonary function tests while on study will be referred to a pulmonologist for consideration of AAT augmentation therapy, which will be provided by the Sponsor if not otherwise available locally and if indicated in the opinion of the treating pulmonologist (See Pulmonary Study Modification Rules in Appendix 2).

- Arrowhead will review all VC, FVC, FEV_1, and DLCO test results on a weekly basis during our Safety Review Team meetings. Pulmonary function test results will be exported directly from the clinical trial database and any resulting decreases consistent with study modification rules (Appendix 2) from baseline will be identified. A query will be sent to the investigator to confirm a pulmonary consultation has been requested and further dosing will be suspended for this patient until the consultation has occurred. Arrowhead's follow up with sites will occur in order to obtain the pulmonologist evaluation.

- **Hepatic Risk:** Fazirsiran targets the hepatic synthesis of AAT. Arrowhead has not seen a pattern of adverse transaminase changes in the AROAAT1001 healthy volunteer single ascending doses/multiple ascending doses study. However, others developing an siRNA for AATD has seen evidence of mild to moderate elevations in transaminases using hepatocyte targeted siRNA conjugates. The cause of these alanine aminotransferase (ALT) changes has been reported as due to off target effects of the siRNA seed region on microRNAs in the hepatocyte. The siRNA sequence of the fazirsiran sense and antisense molecules have been screened for potential mRNA and microRNA homology and sequences with homology were excluded from consideration. Thus, no such off-target effects are anticipated. Multi-dose (3 weekly doses) GLP toxicity studies with fazirsiran in rats demonstrated minimal to slight hepatocellular necrosis at doses of 30, 60, 120, and 300 mg/kg with associated elevations in ALT and aspartate aminotransferase (AST) of <3X control animals. However, there were no such findings in NHPs which are thought to be more representative of human subjects. In addition, these findings were not found in the

chronic toxicology studies (6-month rat study and the 9-month monkey), which administered monthly doses suggesting the longer interval between administration of doses helped prevent this effect. The chronic toxicology study no observed adverse effect levels (NOAELs) are the highest doses tested; 120 mg/kg in rats and 180 mg/kg in NHPs. To mitigate this risk of adverse ALT changes, the proposed study protocol has built in stopping/study modification rules for ALT elevation applicable to patients who may have elevated ALT at baseline. Blood samples will be drawn frequently to evaluate liver injury and liver function. Additionally, the highest planned dose used in this study of 200 mg is approximately 1/42nd (assuming weight-based conversion and a 70-kg subject) of the rat NOAEL of 120 mg/kg and 1/63rd of the monkey NOAEL from chronic GLP toxicology studies.

- **Injection Site AE Risk:** Fazirsiran and other subcutaneously administered modified siRNA drug candidates evaluated in clinical studies have been associated with mild to moderate injection site reactions (ISRs) (e.g., pain, induration, erythema). Adverse events at the injection site (e.g., erythema, pain, etc.) have been reported with administration of fazirsiran in clinical studies and are therefore considered an identified risk. All were deemed to be nonserious and resolved without sequelae. The majority of the ISRs were mild in severity. Other siRNA antisense oligonucleotides in clinical trials have bene associated with usually mild ISRs. This study includes directions for assessing injection site adverse event (AE) intensity based on pre-defined criteria (see Section 10.5.2). Additionally, steps will be taken to minimize ISRs such as rotating injection sites and allowing the fazirsiran solution to come to room temperature prior to injecting.

4.9. Justification for Dose Levels and Dose Intervals

The proposed doses of 100 mg for up to 3 doses and 200 mg for up to 5 total doses is expected to produce substantial PD effect. In the AROAAT1001 healthy volunteer study, doses of 35, 100, and 200 mg yielded substantial serum AAT reductions, with both 100 mg and 200 mg reaching approximately 90% mean serum AAT reduction after multiple doses. Both the 100 mg and 200 mg dose are below the top dose of 300 mg, which was studied as both single and multiple (three) doses in AROAAT1001. In the Phase 1 study, dose levels up to the top dose of 300 mg were well tolerated with no serious or severe AEs reported in the study and no pattern of adverse laboratory changes associated with fazirsiran.

The rationale for the proposed dosing interval is based on the goal of targeting AATD patients exhibiting liver fibrosis with the aim of halting the liver insult and damage produced by polymers as early and effectively as possible. Providing a dose on Day 1 followed by a dose on Day 29 is likely to more rapidly drive hepatic AAT levels to maximally reduced levels (similar to a loading dose strategy) followed by a maintenance dose 12 weeks after the 2nd dose, and dosing approximately quarterly thereafter. This strategy of maximizing ablation of liver AAT early should yield the most benefit to participants in terms of liver Z-AAT protein reduction over the course of the study, while then moving to quarterly dosing should maximize safety by limiting patient exposure to drug. The administration of quarterly dosing thereafter is based on

AROAAT1001 single dose data showing duration of PD activity with rebound in serum AAT levels beginning approximately 12 weeks after dose administration. Approximate quarterly dosing should minimize additional unnecessary dosing and minimize safety risk.

Using a weight-based conversion, 200 mg, the highest dose level planned for this study provides a safety margin of approximately 63-fold and 42-fold (assuming a 70 kg individual) from the respective NOAELs of 180 mg/kg in a 9-month GLP monkey toxicology study and 120 mg/kg in a GLP 6-month rat toxicology study.

5. OBJECTIVE AND STUDY ENDPOINTS

5.1. Study Objective

To evaluate safety and changes in serum and liver Z-AAT levels, changes in liver disease related biomarkers and changes in liver histology in response to fazirsiran in patients with alpha-1 antitrypsin deficiency associated liver disease (AATD).

5.2. 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.

5.3. Secondary Endpoints

- To determine the effect of multiple doses of fazirsiran on circulating levels of Z-AAT alpha-1 antitrypsin over time versus baseline.
- To evaluate the effect of fazirsiran on changes in ALT over time.
- To evaluate the effect of fazirsiran on changes in GGT over time.
- To evaluate the effect of fazirsiran on changes in FIB-4 and APRI over time.
- To evaluate the effect of fazirsiran on changes in PRO-C3 over time.
- To evaluate the effect of fazirsiran on changes in hepatic stiffness based on FibroScan® over time versus baseline (when available).
- To evaluate effect of fazirsiran 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 fazirsiran treated patients.
- To determine the incidence and severity of treatment-emergent adverse events as a measure of the safety and tolerability of fazirsiran.
- To determine the incidence and titers of anti-drug antibodies (ADAs) to fazirsiran.

5.4. Exploratory Endpoints

- To evaluate the effect of fazirsiran 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 fazirsiran (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 fazirsiran 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 fazirsiran 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).

6. STUDY PLAN

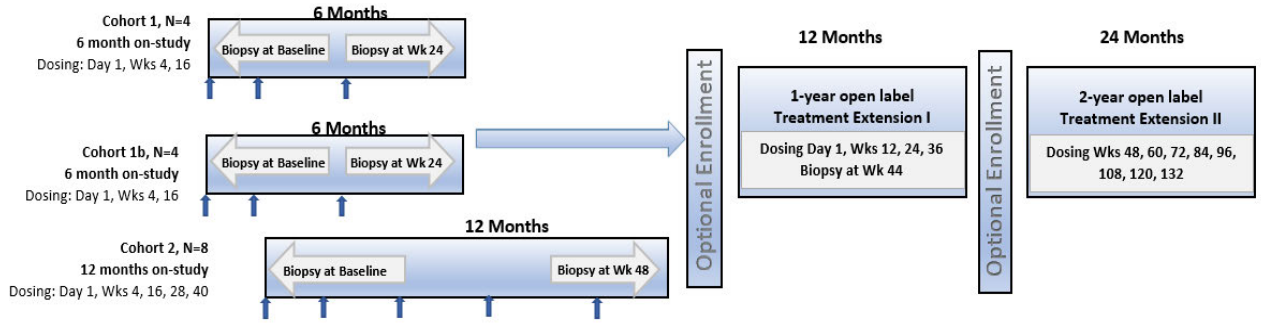
6.1. Study Design

A multi-center, multi-dose, open-label, Phase 2 study will be conducted to evaluate the safety and efficacy of the investigational product, fazirsiran, administered subcutaneously to patients with Alpha-1 Antitrypsin Deficiency. Participants who have signed an Institutional Review Board (IRB)/Ethics Committee (EC) approved informed consent and have met all the protocol eligibility criteria during Screening, will be enrolled in one of three cohorts. All patients will receive a minimum of three 100 mg or 200 mg doses of fazirsiran, depending on the cohort. At the end of the cohort specified treatment period, subjects will be offered the opportunity to continue treatment in the open-label treatment extension periods. Dosing with fazirsiran may continue a minimum of 12 weeks from the previous dose. Subjects who proceed into Treatment Extension I and/or II will continue to receive the dose to which they were assigned at the start of the study. Based on cumulative safety, efficacy, and PD data from the fazirsiran clinical program (clinical studies AROAAT1001, AROAAT2001, and AROAAT2002), a fazirsiran dose (200 mg) was selected by the Sponsor. Following the respective country regulatory and ethics committees' approvals (including local approvals as necessary) of AROAAT2002 protocol amendment v7.0, all ongoing subjects will be consented and informed of the selected dose and subjects in Cohort 1b (100 mg) will begin receiving the selected dose at their next scheduled dosing timepoint.

All patients will undergo liver biopsies per Schedule of Assessments (SOA) or at Early Termination.

Cohort 1, 1b, or 2 participants who drop out for reasons other than an AE considered at least possibly related to drug may be replaced.

Figure 1: Study Design



6.2. Rationale for Study Design

The study is intended to demonstrate that fazirsiran can safely and effectively improve liver histologic parameters as well as other biomarkers of liver disease by reducing intra-hepatic Z-AAT protein levels through an RNAi mechanism in patients with AATD. Cohort 1 and 1b will

assess histologic changes after 3 doses of fazirsiran and Cohort 2, after 5 doses. Tissue samples from liver biopsy will be required to achieve this. Other markers of liver injury such as Metavir (or equivalent fibrosis staging system, see Appendix 3) fibrosis score will also be measured on biopsy. Biopsy will be conducted pre-dose and post-last dose. Participants who finish Cohort 1, 1b, or 2 may elect to enroll in the treatment extension periods. This treatment extension would continue open-label treatment every 12 weeks for twelve additional doses with an optional liver biopsy, following the fourth dose, at Week 44.

The study will enroll PiZZ patients without F4 (or equivalent by other grading scales) cirrhosis but with evidence of F1-F3 (by Metavir or equivalent) liver disease. The PiZZ genotype represents the majority of AATD patients at risk for the development of liver disease and all PiZZ patients should have measurable intra-hepatic Z-AAT protein in biopsy samples.

6.3. Stopping Rules

A decision to stop the trial early or discontinue drug in an individual subject or group of patients may be indicated based on any of the following:

1. In the case of two or more similar (defined as serious adverse events (SAEs) within same System organ Class [SOC]) Serious Adverse Events both considered at least possibly related to fazirsiran, the trial will be put on halt even if the subject(s) is/are not discontinued from the study drug/study. The Principal Investigator and Sponsor will discuss within 3 days of the Sponsor being notified of the 2nd event and within the timeframe of required regulatory agency notification. Available aggregated data will be reviewed to determine if the study remains safe to proceed, should be discontinued or should continue but with amendments. Restart of the trial will require approval of a substantial amendment from the competent authorities.

2. Evaluation and fazirsiran discontinuation rules for elevated ALTs are provided in Appendix 1.

3. Evaluation and fazirsiran study modification/discontinuation rules for declines in pulmonary function are provided in Appendix 2.

4. Subject who becomes pregnant while in the study.

Sponsor or Investigator can discontinue any subject at any time. If such events (as described in #1, #2, or #3 above) occur and the subject is not discontinued from the study, the reason for not discontinuing the subject will be documented. Including, but not limited to the events listed above, the study may be paused to additional dosing to provide time to evaluate safety data and recommend the action to be taken, which may include, but is not limited to, one of the following:

- Discontinuation of a subject or group of patients from the study
- The study is stopped immediately with no further dosing

- The study will continue, but using a lower dose
- The study will continue as planned

6.4. Duration of the Study

For Cohort 1 and 1b, the duration of the study is approximately 36 weeks, from beginning of the Screening period to the End-of-Study (EOS) visit. For Cohort 2, the duration of the study is approximately 60 weeks, from beginning of the Screening period to the EOS visit.

All patients will be invited to continue dosing with fazirsiran beyond the planned EOS visit as part of the treatment extension periods. The total duration of the treatment extension is approximately 144 weeks (36 months, i.e., 3 years). The duration of the study for Cohort 1, 1b and Cohort 2 patients entering the treatment extension is 180 and 204 weeks respectively. In that case, they will receive a total of twelve additional doses of fazirsiran at 12-week intervals. There will be a follow-up telephone call to assess for pregnancy occurrence 12 weeks post-last dose.

7. SUBJECT SELECTION

7.1. Number of Patients & Patient Demographics

This study will be conducted in PiZZ patients with Alpha-1 Antitrypsin Deficiency. Both males and females are eligible, ages 18-75. In total, the study will consist of up to approximately 16 participants. Patients with a history of PiZZ AATD in Cohort 1 will receive three 200 mg doses of fazirsiran, in Cohort 1b will receive three 100 mg doses of fazirsiran and Cohort 2 will receive five 200 mg doses of fazirsiran. At the conclusion of Cohort 1, 1b, or 2, patients who elect to participate in the treatment extension periods will receive twelve additional doses of fazirsiran every 12-weeks.

All eligible patients will require a pre-dose biopsy completed as part of the study within the screening window. Participants will consist of male and female adult PiZZ (based on genotype completed at baseline or from a source verifiable document) alpha-1 antitrypsin patients. Patients previously, currently or never receiving AAT augmentation therapy are eligible for enrollment.

7.2. Inclusion Criteria

To be eligible for enrollment, participants must meet all the following inclusion criteria:

1. Male or non-nursing female patients 18-75 years of age, inclusive, at the time of Screening with previous diagnosis of PiZZ genotype Alpha-1 Antitrypsin Deficiency. PiZZ diagnosis from source verifiable medical records is permitted. Otherwise, patients must undergo PiZZ confirmatory testing at Screening. PiMZ or PiSZ genotypes are not permitted.

2. Able and willing to provide written informed consent prior to the performance of any study specific procedures.

3. A 12-lead electrocardiogram (ECG) at Screening that, in the opinion of the Investigator, has no abnormalities that compromise participant's safety in this study.

4. Non-smoker (defined as does not smoke cigarettes daily for at least 12 months) with current non-smoking status confirmed by urine cotinine at screening and throughout the study. Patients may be on nicotine replacement (patch or gum). E-cigarettes (vapor) are not permitted. A positive urine cotinine result due to nicotine replacement is acceptable for enrollment at the discretion of the Investigator.

5. Participants using highly effective contraception during the study and for 12 weeks following the last dose of fazirsiran. Males must not donate sperm for at least 12 weeks post last dose of study treatment. Females of childbearing potential must have a negative urine pregnancy test at Screening and on Day 1 pre-dose. Females not of childbearing potential must be post-menopausal (defined as cessation of regular menstrual periods for

at least 12 months), confirmed by follicle-stimulating hormone (FSH) consistent with post-menopausal state based on lab reference ranges.

- Using twice the normal protection of birth control by using a condom AND one other form of either birth control pills (The Pill), depot or injectable birth control, IUD (Intrauterine Device), birth control patch (e.g., Ortho Evra), NuvaRing®, OR Surgical sterilization as a single form of birth control: i.e., tubal ligation, hysterectomy, bilateral oophorectomy, vasectomy or equivalently effective surgical form of birth control.

- True subject abstinence for the duration of the study and 12 weeks after the dose of fazirsiran is acceptable only when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea methods are not considered "true" abstinence and are not acceptable methods of contraception.

6. Participants who are willing and able to comply with all study assessments and adhere to the protocol schedule

7. Must have suitable venous access for blood sampling

8. No abnormal finding of clinical relevance at the Screening evaluation that in the opinion of the Investigator could adversely impact subject safety during the study or adversely impact study results.

9. Liver biopsy indicating Metavir F1- F3 (or equivalent on other grading scales, see Appendix 3) liver fibrosis based on local pathologist read. All patients will require a liver biopsy during the screen period except for prior screened patients who now meet the fibrosis criteria as long as there is sufficient material for a baseline assessment as per specifications in the laboratory manual.

All laboratory tests used as inclusion criteria may be repeated once and the repeat value may be used for inclusion purposes. Central labs will be utilized for the study, however local labs may be utilized as necessary due to emergent situations.

7.3. Exclusion Criteria

A potential participant will be excluded from the study if any of the following criteria apply:

1. INR ≥1.5 at Screening. If based on opinion of Investigator and/or prescribing physician patient is appropriate for anticoagulant holiday, patient may stop taking anticoagulant for an appropriate washout period or reversal with vitamin K and if indicated a repeat INR within <1.5 would be acceptable. If INR is not indicated (direct thrombin inhibitors or Xa inhibitors) then appropriate washout period alone may be acceptable. (Note: Anti-platelet

agents such as aspirin, clopidogrel or nonsteroidal anti-inflammatory drugs [NSAIDs] are acceptable but must be held 7 days before and 7 days after liver biopsy)

2. ALT and AST levels >250 U/L at Screening (one retest permitted)

3. Estimated glomerular filtration rate (eGFR) <60 ml/min at Screening (one retest permitted)

4. Post-bronchodilation (if available) FEV_1 <65% of predicted at Screening in any subject **not** receiving AAT augmentation therapy.

5. Post-bronchodilation (if available) FEV_1 <45% of predicted at Screening in any subject currently receiving AAT augmentation therapy on a regular basis and planning to continue AAT augmentation therapy for the duration of the study.

6. Patients expected to have severe and unavoidable high-level exposure to inhaled pulmonary toxins during the study.

7. Patients with recent (last 3 months) diagnosis of pneumonia are also excluded.

8. Human immunodeficiency virus infection, as shown by the presence of anti-HIV antibody (sero-positive)

9. Seropositive for HBV (HBsAg positive at Screening) or HCV (detectable HCV RNA at Screening). Cured HCV (positive antibody test without detectable HCV RNA is acceptable).

10. Uncontrolled hypertension (systolic blood pressure [BP] >170 and diastolic BP >100 mmHg at Screening). Patients may rescreen once BP is successfully controlled.

11. A history of torsades de pointes, ventricular rhythm disturbances (e.g., ventricular tachycardia or fibrillation), heart block (excluding first-degree block, being PR interval prolongation only), congenital long QT syndrome or new ST segment elevation or depression or new Q wave on ECG. Participants with a history of atrial arrhythmias should be discussed with the Medical Monitor

12. Symptomatic heart failure (per New York Heart Association guidelines), unstable angina, myocardial infarction, severe cardiovascular disease (ejection fraction <20%, transient ischemic attack (TIA) or cerebrovascular accident (CVA) within 6 months prior to Screening

13. History of malignancy within the last 1 year except for adequately treated basal cell carcinoma, squamous cell skin cancer, superficial bladder tumors, or in situ cervical cancer. Participants with other curatively treated malignancies who have no evidence of metastatic disease and >1-year disease-free interval may be entered following approval by the Medical Monitor

14. History of major surgery within the prior 1 month prior to Screening

15. Regular use of alcohol within one month prior to the Screening visit (i.e., more than 14 units of alcohol per week [1 Unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol])

16. Use of illicit drugs (such as cocaine, phencyclidine [PCP]) within 1 year prior to the Screening visit or positive urine drug screen at Screening (a urine drug screen positive for benzodiazepines, opioids or marijuana is acceptable for enrollment at the discretion of the Investigator if the positive test is due to a substance used for medical reasons).

17. Use of an investigational agent or device within 30 days prior to dosing or current participation in an investigational study involving a therapeutic intervention. Patients receiving AAT augmentation therapy as part of a post-marketing study or other access program for approved therapies are acceptable.

18. Blood donation (≥500 mL) within 7 days prior to study treatment administration.

19. Any concomitant medical or psychiatric condition or social situation that would make it difficult to comply with protocol requirements or put the participant at additional safety risk. Patients with NASH, NAFLD, metabolic syndrome, well controlled diabetes mellitus (even if on insulin) or hemochromatosis are acceptable if disease is stable and does not pose a significant threat to subject participation. Patients enrolled with NASH should have no plans to undergo bariatric surgery or initiated pharmaceutical therapy for NASH (such as Vitamin E or pioglitazone) during the course of the study. If already on such treatment, regimen must be stable for at least 12 weeks.

20. A history of thromboembolic disease (including deep vein thrombosis or pulmonary embolism), myocardial infarction, stroke within six (6) months of screening.

21. Participants who are unable to return for all scheduled study visits.

22. Females of childbearing potential who are breastfeeding.

23. Any other condition, that in the opinion of the Investigator would render the participant unsuitable for enrollment or could interfere with participating in and completing the study.

24. Previous diagnosis of decompensated liver cirrhosis or complications of cirrhosis (e.g., varices, ascites, hepatic encephalopathy) based on source verifiable medical record.

25. Diagnosis of F4 (Metavir) or similar grading scale equivalent indicating definitive cirrhosis on pre-dose liver biopsy completed as part of the AROAAT2002 study based on local pathologist read or based on historical liver biopsy (last 6 months from consent) with a source verifiable pathologist read of definitive liver cirrhosis.

Note: Sponsor Medical Monitor has the option to exclude the enrollment of a participant if, based upon the participant's medical history or Screening results, it is felt that a participant's safety may be at risk.

All laboratory tests used as exclusion criteria may be repeated once and the repeat value may be used for exclusion purposes. Central labs will be utilized for the study, however local labs may be utilized as necessary due to emergent situations.

7.4. Participant Withdrawal Criteria

Participants will be advised that they are free to withdraw from the study at any time for any reason or, if necessary, the Investigator, or medically trained designee, may withdraw a participant from the study, per the following criteria, to protect the participant's health:

- the need to take medication which may interfere with study measurements;
- intolerable/unacceptable adverse experiences;
- major violation of or deviation from study protocol procedures;
- non-compliance of participant with protocol;
- participant unwilling to proceed and/or consent is withdrawn; or
- withdrawal from the study if, in the Investigator's judgement, it is in the participant's best interest.
- pregnancy

The reasons for withdrawal will be recorded on the case report form (CRF) and included in the final clinical study report, along with any adverse events and any necessary medical treatment.

If a participant is withdrawn from the study due to significant AE or SAE, the Investigator, or medically trained designee, will evaluate the urgency of the event. If the situation warrants, the Investigator, or medically trained designee, will take appropriate diagnostic and therapeutic measures. If the situation is not an immediate emergency, the Investigator, or medically trained designee, at the clinical study facility will attempt to contact the Arrowhead Pharmaceuticals, Inc. Medical Monitor or medically qualified designee for consultation. No medical help, diagnosis, or advice will be withheld from the participant due to an inability to contact the Medical Monitor. The participant will be encouraged to remain available for follow-up medical monitoring. The Sponsor will be notified as soon as possible of any participant withdrawals. The Investigator should report all pregnancies and pregnancies in partners of subjects within 24 hours of awareness of the pregnancy using the Pregnancy Notification Form. This completed form should be emailed to Labcorp, the pharmacovigilance vendor for this study at:

Arrowhead.Safety@Labcorp.com or fax to: 1-626-628-1882

Participants who are withdrawn or discontinue prior to EOS visit for reasons other than an AE considered at least possibly related to drug, may be replaced.

7.5. Restrictions and Concomitant Medications

1. ***Study Visit Duration:*** For each participant, clinic visits will last approximately 3 hours total, 2 hours pre-dose and 1hour post-dose on dosing days. Participants will return to the clinical facility for out-patient visits as per SOA. Participants will be observed post-dose for approximately 2 hours or as clinically indicated as per the Investigator. ***Fasting:*** On the day of dosing, participants will fast from food for at least 2 hours prior to study treatment administration and 2 hours post dose. Duration of site stay for days when liver biopsy is completed is site dependent.

2. ***Recreational Drugs, Smoking & Alcohol:*** Participants will be instructed to abstain from consuming alcohol for at least 48 hours prior to their clinic visit on dosing days, and during the clinic visit. In addition, participants will be instructed to refrain from regular use of alcohol (i.e., more than 14 units of alcohol per week [1 Unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]) for the study duration. Participants must abstain from use of recreational drugs throughout the study. Participants must be non-smokers entering the study (as per Inclusion & Exclusion criteria) and abstain from smoking tobacco (including e-cigarettes) for the duration of the study. Nicotine patches or gum is acceptable.

3. ***Concomitant Medications*:** Continuation of medications, vitamins and supplements deemed medically indicated is acceptable. Otherwise, allowance of concomitant medications will be at the discretion of the study Investigator in consultation with Sponsor Medical Monitor (when necessary). Augmentation therapy is permitted. Procedural sedation with benzodiazepines or equivalent during liver biopsy as needed is permitted. Standard of care for chronic obstructive pulmonary disease (COPD) including bronchodilators, corticosteroids and other modalities are permitted.

8. INVESTIGATIONAL PRODUCT

8.1. Description, Identification and Dosage

Arrowhead Pharmaceuticals, Inc. is responsible for the supply of fazirsiran together with detailed instructions (in a Pharmacy Manual) describing preparation of fazirsiran (TAK-999, also referred to as ARO-AAT).

Accordingly, fazirsiran will be supplied as single sterile 2-mL vials containing fazirsiran, with the correct dose of fazirsiran prepared by the Pharmacy prior to dosing participants.

Each dose of fazirsiran will be administered by subcutaneous injection. The injection volume is 0.43 mL for 100 mg and 0.87 mL for 200 mg and should be administered as a single injection. Injections will be made into the subcutaneous tissue at an appropriate site (e.g., abdomen, thigh, upper arm, etc.) using a 25-30 Gauge, ½ inch needle. The abdomen is the preferred site. The injection site is to be varied (no multiple injections into the same exact site. Alternating various locations on the abdomen is acceptable) and injection site location is to be recorded in the electronic Case Report Form (eCRF). Prior to dose administration, the fazirsiran vial must be allowed sufficient time to come to room temperature. Do not inject into areas of active skin disease or injury such as sunburns, skin rashes, inflammation or skin infections.

8.2. Supply, Preparation, Storage and Labelling of Fazirsiran

Fazirsiran Injection is a ready to use injection preparation for subcutaneous administration and is supplied as a sterile Type-1 glass 2-mL vial (1.1 mL nominal volume, 1.0 mL withdrawable volume). The clinical drug product is labeled: ARO-AAT Injection.

Strength: 230 mg/mL

Appearance: Clear, colorless to yellow solution

Inactive ingredients: 0.5 mM sodium phosphate monobasic, 0.5 mM sodium phosphate dibasic in water for injection

Shipment and Storage: Refrigerated, 2 to 8 °C

The fazirsiran dose will be prepared, per the Pharmacy Manual instructions, by a Pharmacist or qualified staff at the clinical sites. Aseptic technique will be used throughout dose preparation ensuring sterility of the solution. Because the fazirsiran vial must come to room temperature before administration, the time the vial is removed from the refrigerator and the time of administration must be documented to demonstrate administration within drug stability boundaries.

Fazirsiran has been shown to be stable and compatible with the clinical administration components. Please refer to the Pharmacy Manual for more detailed instructions.

The investigational product vials will be labeled per current Good Manufacturing Practice (cGMP)/Good Clinical Practice (cGCP).

Fazirsiran will be stored at clinical sites securely under the appropriate conditions.

8.3. Study Drug Handling

The Sponsor will provide the Investigator with a sufficient quantity of clinical drug supplies. The Investigator must ensure that deliveries of investigational product from the Sponsor are correctly received by a responsible person, that all receipts of drug shipments are recorded on the appropriate Drug Accountability forms prepared by the pharmacy at the clinical site and that the products are stored in a secure area under recommended storage conditions. It is also the responsibility of the Investigator to ensure that the integrity of packaged study product is not jeopardized prior to dispensing.

Only participants enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer study drug. The study drug must be stored in a secure area with access limited to the Investigator and authorized staff and under the physical conditions that are consistent with the study drug-specific requirements.

An authorized and trained staff member at each clinical trial site will dispense the study drug per pre-defined drug dispensing requirements. The dispensing and administration will be verified by a second member of site staff.

Fazirsiran will be supplied by Arrowhead Pharmaceuticals, Inc. and labeled with the drug name, batch number, expiration date (as applicable) and storage conditions. Individual doses will be dispensed by clinical trial site staff members on the morning of dosing and recorded in the drug accountability records. A Pharmacy Manual will be prepared to define the procedures for dispensing.

Standard Operating Procedures will be followed for the receipt, handling and accountability of the study formulations.

8.4. Accountability of Study Supplies

All material supplied is for use only in this clinical study and should not be used for any other purpose. The Investigator is responsible for the investigational product accountability, reconciliation and record maintenance at the investigational site. In accordance with all applicable regulatory requirements, the Investigator or designated site staff must maintain investigational product accountability records throughout the course of the study. This person will document the amount of investigational product received from Arrowhead Pharmaceuticals, Inc. and the amount administered to participants. A Clinical Research Associate (CRA) will perform initial and ongoing study drug accountability. Used vials of fazirsiran will be retained sequestered per participant (where allowable by local policy) and made available to the CRA during study drug reconciliation.

A Drug Dispensing Log must be kept current and will contain the following information:

- the identification of the participant to whom the drug was dispensed; and
- the date(s) and quantity of the drug dispensed to the participant.

The date and time of dose preparation and release will be maintained to support administration of study drug. The Pharmacy will dispense the study medication and the study center will administer the study medication only to participants included in this study following the procedures set out in the study protocol and Pharmacy Manual. Each participant will be given only the study medication carrying his/her study number. Study drug administration will be documented on the CRFs and/or other study drug record. The inventory must be available for inspection by the monitor during the study. Drug supplies, excluding partially used or empty containers, will either be collected at the end of the study by the study monitor or returned by the Investigator or designee to Arrowhead Pharmaceuticals, Inc. When requested in writing by the Sponsor, following drug accountability and reconciliation, unused drug supplies may be destroyed by the Investigator or designee provided such disposition does not expose humans to risks from the drug and is permitted per the site's Standard Operating Procedures. Records shall be maintained by the Investigator of any such alternate disposition of the test drug. These records must show the identification and quantity of each unit disposed of, the method of destruction (considering the requirements of local law), and the person who disposed of the test substance. Such records must be submitted to the Sponsor.

8.5. Retention of Investigational Product Vials

For this study, used and partially used drug vials will be retained for an adequate period to allow accountability by the CRA. No additional study drug samples will be retained.

8.6. Allocation to Treatment

All potential participants who sign an informed consent at Screening will receive a unique 6-digit number (i.e., a Screening Number). The first 3 digits will represent the assigned site number and will be the same for each participant that screens at an individual site. The next 3 digits will be assigned sequentially (starting with 001). For patients who are deemed eligible, this 6-digit screening number will become the subject's permanent study ID number.

Participants who drop out for reasons other than an AE considered at least possibly related to drug may be replaced.

9. STUDY METHODS AND SCHEDULES

9.1. Overview of Procedures

A multi-center, multi-dose, open-label study will be conducted to evaluate the safety, tolerability and effect on liver histology of the investigational product, fazirsiran, administered subcutaneously to patients with Alpha-1 Antitrypsin Deficiency. Participants who have signed an IRB/EC approved informed consent and have met all the protocol eligibility criteria during Screening, will receive multiple subcutaneous doses of fazirsiran.

Participants will undergo the following evaluations at regular intervals during the study (refer to the SOA): medical history, physical examinations, vital sign measurements (blood pressure, temperature, heart rate, respiratory rate), weight (at baseline), adverse events monitoring, ECGs, urine pregnancy test/FSH (females), concurrent medication, pulmonary function testing (spirometry including VC, FVC, FEV_1, FEV_1/VC, FEV_1/FVC, and DLCO) and sample collection for hematology, coagulation, biochemistry, cardiac troponin, urinalysis, urine cotinine, anti-drug antibodies, drug screens, serum alpha-1 antitrypsin levels (where applicable), serum fibrosis biomarkers, liver biopsy, MRE (where feasible and available) and FibroScan® (where available).

Study visits will occur during the Screening window (Day -56 to -1), and as per the SOA. A telephone follow-up will occur 12 weeks after the last dose to assess for pregnancy occurrence. Clinically significant changes including adverse events will be followed until resolution is achieved, or until medically stable or the event is otherwise explained, or until the participant is lost to follow-up.

Baseline values will be those assessments obtained pre-dose and in the closest proximity to the first dose.

Participants will fast from food for at least 2 hours pre-dose and 2 hours post-dose. Refer to the SOA for additional information.

The Investigator (or medically qualified designee) will be required to remain within the clinical study facility for 2 hours after dosing on Day 1 and will remain on call for the duration of the study.

9.2. Selection and Screening

Prior to commencement of any screening procedures, the Investigator, or designee, will inform the participant about the nature and purpose of the study, including the risks and benefits involved, possible AEs, the fact that their participation is voluntary and provide a copy of the IRB/EC-approved Informed Consent Form for review. Each participant will acknowledge receipt of this information by giving written informed consent for their involvement in the study in the presence of the Investigator, or designee, who will also sign and date the Informed Consent Form. Time of consent will be recorded on the Informed Consent Form or in the source documents for the subject. The original signed consent form will be retained by the Investigator

and a copy of the original will be given to the participant. Informed consent will be performed per the Principles of the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) procedures.

Having given Informed Consent, potential participants will undergo procedures outlined in the SOA, to be performed within 56 days of the scheduled dosing date, to determine that they meet the inclusion/exclusion criteria specified in Section 7.2 and Section 7.3.

9.3. On-Study Procedures/Assessments

9.3.1. Study Procedures: Clinical Facility Confinement

Eligible participants will attend the Clinical Facility on Day 1. Note that study dose administration is on Day 1, which must occur within 56 days of Screening. Participants will be confined to the clinical facility for approximately 2 hours pre-dose and 1hour post-dose.

On arrival at the clinical facility on Day 1, the Investigator, or designee, will meet with the patient to reiterate all study procedures and encourage the patient to ask any questions. All participants shall undergo a check-in procedure during which questions will be asked regarding protocol compliance and safety monitoring.

Documentation of the participant's fulfillment of the entry criteria, for all participants considered for the study and subsequently included or excluded, is to be completed by the Investigator, or medically qualified designee. Documentation of screening failure details will be recorded using eligibility screening forms or a participant screen failure log. Procedures outlined in the SOA will be performed. Timing will abide by fasting restrictions outlined Section 7.5.

On days when biopsy is completed, duration of confinement at the site is dependent on-site specific policies and procedures related to monitoring post-procedure. If such policies or procedures do not exist, timing for post-biopsy monitoring is at the discretion of the Investigator.

9.3.2. Demographics/Medical History

Medical History will include medication use over the previous 30 days, including vitamins, over-the-counter, prescription drugs, recreational drugs or supplements (such as protein powder or creatine) and alcohol and tobacco use.

9.3.3. Physical Exam

A complete physical exam will be performed at Screening and as per the SOA. At Screening, height (centimetres, without shoes) and weight (kilograms, without shoes) will be obtained to determine body mass index (BMI). At all other time-points outlined in the SOA, a symptom-directed physical exam will be performed if indicated.

9.3.4. Pulmonary Function Testing

Spirometry and DLCO will be conducted at time-points outlined in the SOA for all participants. When conducted on dosing days, spirometry and DLCO are to be conducted pre-dose. Spirometry will be conducted in a pulmonology laboratory or at the clinical site in accordance with American Thoracic Society and European Respiratory Society (ATS-ERS) guidelines (Graham et al., 2019) and each patient will undergo pulmonary function testing at the same location throughout the study. DLCO assessment will be conducted in accordance with ATS-ERS guidelines (Graham et al., 2017). All spirometry and DLCO values collected and recorded will include both pre- and post-bronchodilation measurements (unless contraindicated or unavailable). Spirometry and DLCO should also be conducted at any time a patient experiences a COPD exacerbation.

Spirometry: Spirometry will include VC, FVC, FEV_1, FEV_1/VC, and FEV_1/FVC, all of which will be recorded in the eCRF.

Bronchodilator: At least 3 pre-bronchodilator maneuvers will be performed, followed by administration of a bronchodilator (generally 90 µg albuterol per puff or 100 µg salbutamol per puff), unless contraindicated or unavailable. A site may elect to not perform bronchodilation on certain study subjects if that is in accordance with the site's standard of practice. Following the administration of the bronchodilator, at least 3 post-bronchodilator maneuvers will be performed.

The best pre- and post-bronchodilation measurements should be documented in an eCRF as follows:

- The best FEV_1 is the largest volume FEV_1 from an acceptable maneuver
- The best FVC is the largest volume FVC from an acceptable maneuver
- The best FEV_1/FVC is the best FEV_1 divided by the best FVC, even if these values come from different maneuvers

The number of puffs of bronchodilator administered should be documented, as this information will be captured on the pulmonary function testing eCRF. If administration of bronchodilator during spirometry is not aligned with the institution's practice, the CRA will be notified to ensure Sponsor notification and appropriate study file documentation.

DLCO: The DLCO assessment may be performed either pre- or post-bronchodilation. At least 2 maneuvers should be attempted. The DLCO value recorded in the eCRF should be the average of 2 or more acceptable, repeatable maneuvers.

9.3.5. Electrocardiogram

A single 12-lead ECG measurement will be obtained at time-points outlined in the SOA after the participant is supine or semi-supine (same position each time is preferred) for at least 3 minutes. Any clinically significant abnormal ECGs will be repeated in triplicate, with each measurement

approximately 1 minute apart. ECGs will be performed prior to venepuncture and other invasive procedures.

9.3.6. Vital Sign Assessments

Systolic/diastolic blood pressure, temperature, heart rate, respiratory rate (breaths/min) will be obtained at time-points outlined in the SOA after the participant is seated or semi-supine (same position each time is preferred) for at least 3 minutes. Vitals signs will be obtained prior to venepuncture and other invasive procedures.

9.3.7. Clinical Laboratory Tests

Blood and urine samples will be collected to perform clinical laboratory tests. Participants will be required to fast for at least 2 hours for the screening sample collections.

At the screening visit, up to 56 days prior to the first dose of study medication, a blood and urine sample will be collected for the laboratory tests detailed below, to establish baseline data and eligibility for enrolment. The results will be assessed by the Investigator, or medically qualified designee, before study enrolment. Any abnormality in laboratory values (that are confirmed on repeat) deemed clinically significant by the Investigator, or medically qualified designee (i.e., those that would jeopardize the safety of the participant or impact on the validity of the study results), will result in exclusion of that participant. Clinical laboratory tests will be performed on participants' blood and urine at specified time-points listed in the SOA.

***Biochemistry*:** Sodium, potassium, chloride, bicarbonate, glucose, urea, creatinine, eGFR, creatine kinase, uric acid, phosphate, total calcium, anion gap, total cholesterol, albumin, globulins, protein, total bilirubin, conjugated bilirubin, gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LD), triglycerides, C-reactive protein, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, Triglycerides and Troponin I.

Hematology: Hemoglobin, red blood cell (RBC) count, hematocrit, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), platelets, white cell count, neutrophils, lymphocytes, monocytes, eosinophils and basophils.

Coagulation: Partial thromboplastin time (PTT), Prothrombin time with INR and Fibrinogen.

Urinalysis: Leucocytes, nitrites, urobilinogen, protein, pH, blood, specific gravity, ketone, bilirubin and glucose.

Urine Cotinine: Urine cotinine levels (at Screening and throughout the study) to confirm non-smoking status.

Microscopic Urinalysis will be Performed if Indicated: White Blood Cells, RBCs, Epithelial cells, Bacteria.

Serology: Hepatitis B surface antigen, Hepatitis C antibody (with HCV RNA as confirmatory test if needed for positive antibody test) and HIV antibody screen. If necessary, participants will be counseled by the Investigator, or medically trained designee, concerning the blood tests for Hepatitis B surface antigen, Hepatitis C and HIV antibodies, and their subsequent results.

FSH: Post-menopausal status will be confirmed by follicle-stimulating hormone (FSH) level consistent with post-menopausal state.

Drugs Screen: Urine drug screen for Benzodiazepines, Amphetamines, Barbiturates, Methamphetamines, Methadone, Opiates, Phencyclidine, Cannabinoids, Ecstasy and Cocaine.

Pregnancy: Females of childbearing potential will have a urine pregnancy test. If the urine pregnancy test is positive, the patient will not be dosed and will be referred to their primary care provider for follow up.

Anti-drug Antibody (ADA): Serum will be collected to assess for presence of fazirsiran antibodies.

9.3.8. Pharmacodynamics

Alpha-1 Antitrypsin Level: Alpha-1 antitrypsin levels will be measured as per the SOA and per Laboratory Manual. Samples will be analyzed by standard clinical laboratory assay for alpha-1 antitrypsin levels and Z-AAT levels using a Z-specific assay.

Liver Biopsy: Pre-dose and post-dose percutaneous liver biopsies will be conducted to obtain tissue samples for liver Z-AAT levels and histological evaluation. Procedure detail and tissue processing protocols are outlined in the Laboratory Manual.

Fibrosis Markers: Markers of liver fibrosis including PRO-C3, PRO-C6 (if feasible) as well as calculated values for aspartate aminotransferase-to-platelet ratio index (APRI) and FIB-4 will be assessed.

Magnetic Resonance Elastography (MRE): Pre-dose and post-dose per the SOA liver stiffness using will be evaluated using MRE standard procedures (optional).

FibroScan®: Pre-dose and post-dose per the SOA liver stiffness will be evaluated using FibroScan® standard procedures (if available at site).

9.3.9. Concomitant Medications/Therapies

Participants will be instructed to inform the Investigator of the details (indication, dose and dates of administration) if they do take any medication, and these details will be recorded in the CRF. Allowance of concomitant medications will be at the discretion of the study Investigator in consultation with Sponsor Medical Monitor (when necessary). Augmentation therapy is permitted. Start date and dose of augmentation therapy should be captured. Sedation with benzodiazepines or alternatives is acceptable during liver biopsy. Continued use of medications to treat chronic conditions (including COPD) are acceptable.

9.3.10. Follow-Up Procedures: 12 Week Post Last Dose Telephone Call

Document telephone contact with each participant to verify compliance with contraceptive measures and absence of any known pregnancy.

9.3.11. Early Termination Procedures

The reason for Early Termination will be documented in source documents and eCRF. Procedures as outlined in the SOA will be completed.

9.4. Study Formulation Administration

Appropriately trained employees of the clinical site will administer the study treatment. Each dose will be administered as a single subcutaneous injection. The date, time, and location of administration will be recorded in the source notes and witnessed by a second person from the clinical facility. The preferred site of injection is the abdomen. Optional additional sites are the upper arms and thighs.

Table 5: Injection Volume per Dose Level

Dose	Concentration	Total Injection Volume	# Injections per planned dose
100 mg	230 mg/mL	0.43 mL	One
200 mg	230 mg/mL	0.87 mL	One

9.5. Timing of Treatments and Procedures

The visits following Day 1 are listed in the SOA. A post-dose visit is to be conducted 24 to 48 hours after the first three fazirsiran administrations. A visit specified as Week X has a target date of Day 1+X number of weeks, for example, the Week 4 visit ideally occurs 28 days after Day 1 (on Day 29). In Treatment Extension I, the calendar resets and Day 1 will be the first dose received during the treatment extension periods (approximately 12 weeks after the last dose in either Cohort 1, 1b, or 2) although the subject may have received previous doses while participating in Cohort 1, 1b, or 2.

Actual times of procedures for each participant will vary depending on scheduling and will be recorded in the CRF.

Post-dose time-points will be determined from the end of the injection/administration.

In the event of multiple procedures scheduled at the same time, non-invasive procedures (i.e., ECGs, AE assessment) will be conducted prior to invasive procedures (i.e., blood sample collection). Timing of activities may be adjusted slightly to accommodate all procedures.

The following windows are allowed for study assessments/visits:

Pre-dose:	Within three (3) hours prior to dosing
All other procedures through 2 hours:	±15 minutes

See the SOA for treatment windows.

9.6. Safety Assessments

The safety of fazirsiran will be evaluated by collection of the following measurements performed at specified time-points:

- Monitoring of AEs/SAEs
- Physical examinations
- Vital signs
- ECG measurements
- Injection Site Reactions
- Clinical laboratory tests (hematology, biochemistry, cardiac troponin, coagulation, urine cotinine and urinalysis)
- Concomitant medications/therapy, and
- Reasons for treatment or study discontinuation due to toxicity
- Pulmonary Function Testing including spirometry (including VC, FVC, FEV_1, FEV_1/VC, and FEV_1/FVC,) and DLCO. Changes in VC, FVC, FEV_1, and DLCO between pre-dose and all post-dose evaluations will be analyzed.
- Number and severity of COPD exacerbations based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria will be evaluated as an AE of special interest.

The AE/SAE reporting period for an enrolled participant will begin when the participant provides informed consent. Treatment-Emergent AEs/SAEs will be those defined as following dose administration through EOS or Early Termination. All AEs/SAEs that occur during the AE reporting period specified in the protocol must be reported to Arrowhead Pharmaceuticals, Inc., regardless of the relationship of the AE to study treatment. Any known untoward event that occurs beyond the AE reporting period that the Investigator considers an SAE and possibly related to study treatment will be reported to Arrowhead.

9.7. Blood Sampling for Pharmacodynamic Analysis

Blood samples will be collected from participants through an indwelling cannula or through a fresh vein puncture. The actual blood collection time will be recorded in the source documents. All deviations outside the range allowed above will be documented as protocol deviations. In all such cases, appropriate time corrections, for the actual time of sample collection will be incorporated at the time of data analysis. Blood samples will be collected at time-points outlined in the SOA.

The target sample times will be printed in the CRFs. The actual sample times (times samples taken) will be recorded alongside the nominal times in the CRF and will be entered at the time of or as soon as possible after sampling. All times must be recorded in the 24-hour format. An explanation must be given for any blood sample taken outside of the set sampling times.

9.7.1. Sample Processing and Analysis for Pharmacodynamic Samples

Pharmacodynamic (AAT):

Serum alpha-1 antitrypsin samples will be drawn and analyzed by standard clinical laboratory assay for alpha-1 antitrypsin levels and Z-AAT levels using a Z-specific assay. Left over serum from AAT blood draws will be frozen as back up samples.

Whole blood will be collected and processed per the Laboratory Manual.

Results, percent change, and duration of response from baseline to timepoints specified in the SOA will be analyzed and summarized by cohort and whether or not on augmentation.

10. ADVERSE EVENTS

The Investigator and clinical facility staff are responsible for detection, recording and reporting of events that meet the criteria and definition of various adverse events as listed below. Adverse events will be recorded from time of signed consent through to end of study; only AEs that occur post-dose will be considered treatment-emergent. The Investigator and clinical facility staff are responsible for detection, recording and reporting of pregnancy and appropriate follow up. The Investigator should report all pregnancies and pregnancies in partners of subjects within 24 hours of awareness of the pregnancy using the Pregnancy Notification Form. This completed form should be emailed to Labcorp, the pharmacovigilance vendor for this study at:

Arrowhead.Safety@Labcorp.com or fax to: 1-626-628-1882

10.1. Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or diagnostic test), symptom, or disease temporally associated with the use of a medicinal (investigational/experimental) product, whether related to this product or not. (Refer to ICH E2a: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, 27 October 1994).

Treatment emergent AEs will be defined as AEs with onset after administration of the study drug, or when a preexisting medical condition increases in severity or frequency after study drug administration.

AEs will not include:

- A medical or surgical procedure such as surgery, endoscopy, tooth extraction, or transfusion (although the condition that leads to the procedure may be an AE)
- A pre-existing disease or condition present at the start of the study that does not worsen during the study
- Any situation where an untoward medical occurrence has not occurred (for example, hospitalizations for cosmetic elective surgery or “social” admissions)
- An overdose of either the investigational product or a concurrent medication without any resulting signs or symptoms.

A **Serious Adverse Event (SAE)** is an AE that:

- Results in death,

- Is life-threatening, (NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event/reaction in which the participant was at immediate risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death, if it were more severe)
- Requires inpatient hospitalization or prolongation of an existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect.
- Is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations, should be considered serious such as important medical events that may not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require medical or surgical intervention to prevent one of the other serious outcomes listed in the above definition. These should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.2. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs

Abnormal assessments (e.g., ECGs and vital signs) that are judged by the Investigator as clinically significant or result in clinical sequelae will be recorded as AEs. Laboratory abnormalities will be reported by the Investigator as AEs if the abnormality is considered clinically significant or result in clinical sequelae. Laboratory abnormalities not reported as AEs are not to be reported as clinically significant (CS) in the study database.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs.

The Investigator (or medically qualified designee) will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory result or other abnormal assessment is clinically significant.

10.3. Timing, Frequency, and Method of Detecting AEs

Any pre-existing conditions or signs and/or symptoms present in a participant prior to the start of the study (i.e., before informed consent) should be recorded as Medical/Surgical History.

All AEs occurring after informed consent and on or before the final visit must be reported as AEs; only AEs that occur post-dose will be considered treatment-emergent. All AEs must be recorded irrespective of whether they are considered drug-related.

At each visit/assessment in the period defined above, AEs will be evaluated by the Investigator (or medically qualified designee) and recorded in the medical notes and eCRF.

10.4. Recording of AEs

When an AE occurs, it is the responsibility of the Investigator or medically qualified designee to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The Investigator or medically qualified designee will then record the AE on the AE CRF. Additional reporting requirements for an AE meeting serious criteria are discussed in Section 10.7 below.

The Investigator or medically qualified designee will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In all cases, when available, the diagnosis should be reported as the event and not the individual signs/symptoms. It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the appropriate AE CRF pages.

10.5. Evaluating AEs

10.5.1. Assessment of Intensity

The Investigator, or medically qualified designee, will assess intensity for each AE reported during the study. The assessment will be based on the Investigator's (or medically qualified designee's) clinical judgment. The intensity should be assigned to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 10.1.

10.5.2. AEs at the Injection Site

AEs at the injection site (or ISRs) only include AEs at the site of Fazirsiran Injection. AEs at the injection site will be assessed as either Mild, Moderate or Severe:

- Mild: Tenderness with or without associated symptoms (e.g., warmth, erythema, itching), mild pain or mild edema.
- Moderate: Moderate to significant pain or lipodystrophy.
- Severe: Tissue ulceration or necrosis with associated severe tissue damage or if operative intervention is indicated

10.5.3. AEs of COPD Exacerbation

AEs reported as an exacerbation of COPD will be assessed as either Mild, Moderate or Severe according to the GOLD criteria provided below:

- Mild: Treated with short acting bronchodilators only
- Moderate: Treated with short acting bronchodilators plus antibiotics and/or oral corticosteroids
- Severe: Patient requires hospitalization or visits the emergency room. Severe exacerbations may also be associated with acute respiratory failure.

10.5.4. Assessment of Causality

The Investigator (or medically qualified designee) is obligated to assess the relationship between investigational product and the occurrence of each AE. The Investigator (or medically qualified designee) will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The Investigator (or medically qualified designee) will also consult the Investigator's Brochure in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial SAE report. However, it is very important that the Investigator (or medically qualified designee) always assess causality for every event prior to transmission of the SAE report form. The Investigator (or medically qualified designee) may change his/her opinion of causality considering follow-up information, amending the SAE report form accordingly. The causality assessment is one of the criteria used when determining global regulatory reporting requirements.

The Investigator (or medically qualified designee) will provide the assessment of causality utilizing three possible categories: Not Related, Possibly Related and Probably Related.

An AE will be considered "Not Related" to the use of the product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the product and the onset of the AE (e.g., the event occurred either before, or too long after administration of the product for it to be considered product-related).
- A causal relationship between the product and the AE is biologically implausible (e.g., death as a passenger in an automobile accident).
- A clearly more likely alternative explanation for the AE is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related event).
- AE is more likely related to and temporally associated with a procedure (such as liver biopsy).

An AE will be considered "Possibly Related" when there is a reasonable possibility that the incident, experience, or outcome may have been caused by the product under investigation.

An AE will be considered "Probably Related" when there are facts, evidence, or arguments to suggest that the event is related to the product under investigation.

10.6. Follow-up of AEs

After the initial AE, the Investigator is required to proactively follow each participant and provide further information on the participant's condition as deemed appropriate.

All AEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up. Once resolved, the appropriate AE CRF page and SAE report form (if event is serious) will be updated. The Investigator, or medically qualified designee, will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. In the event of a fatal outcome in an SAE, the Investigator, or medically qualified designee, will attempt to obtain postmortem findings, including histopathology, and provide all additional information in a follow up SAE report.

New or updated information regarding an SAE will be recorded on a new SAE report form marked as follow-up with the appropriate follow-up number added to the report. The follow-up report will be signed and dated by the Investigator.

10.7. Prompt Reporting of SAEs

AEs meeting serious criteria MUST be reported promptly to the designated Pharmacovigilance Contract Research Organization (CRO), and the EC.

10.7.1. Completion and Transmission of the SAE Reports

Once an Investigator becomes aware that an SAE has occurred in a study participant, she/he will report the information on an SAE report form to the designated Pharmacovigilance CRO within 24 hours. The SAE report form will always be completed as thoroughly as possible with all available details of the event and signed by the Investigator (or medically qualified designee). If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before reporting the event. The SAE report form will be updated when additional information is received.

The Investigator (or medically qualified designee) will always provide an assessment of causality at the time of the initial report as described in Section 10.5.4.

Facsimile or email transmission of the SAE report form are the preferred methods to transmit this information to the designated Pharmacovigilance CRO. In rare circumstances, notification by telephone is acceptable, with a copy of the SAE CRF sent by overnight mail. Initial notification via the telephone does not replace the need for the Investigator, or medically qualified designee, to complete and sign the SAE report form within the outlined time frames.

The Sponsor will provide a list of project contacts for SAE receipt, fax numbers, telephone numbers, and mailing addresses. Any event that in the opinion of the Investigator may be of immediate or potential concern for the participant's health or well-being will be reported to the Sponsor emergency contact listed below.

Sponsor Emergency Contact
[redacted]

10.7.2. Serious Adverse Event Reports to the EC

The Investigator, or responsible person per local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the EC.

10.7.3. Pregnancy Reporting

Pregnancy occurring in a subject or in the female partner of a male subject during the study must be reported on a pregnancy reporting form to Labcorp, the pharmacovigilance vendor for this study immediately and not later than 24 hours of initially becoming aware of the pregnancy by the Investigator.

Pregnancy data will be collected at the initial notification, birth/termination of pregnancy, and for up to 1 year after birth or until the end of the pregnancy.

Pregnancies are not considered SAEs. However, any SAE that occurs during pregnancy (e.g., serious maternal complications, therapeutic or spontaneous abortion, ectopic pregnancy, stillbirth, etc.) must be reported in accordance with the procedure for reporting SAEs.

10.8. Regulatory Requirements for Reporting of SAEs

The Investigator (or medically qualified designee) will promptly report all SAEs in accordance with the procedures detailed in Section 10.7. Prompt notification of SAEs by the Investigator (or medically qualified designee) **is essential** so that the Sponsor may comply with its regulatory obligations.

The Sponsor will comply with all reporting requirements as stipulated in European Directive 2001/20/EC and in accordance with other national regulations outside the EU as appropriate. The Sponsor is responsible for reporting all suspected unexpected serious adverse reactions to the Eudravigilance database. An adverse **reaction**, in contrast to an adverse **event**, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected. The Sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee, and in any case no later than seven days after knowledge by the Sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days. All other suspected serious unexpected adverse reactions will be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the Sponsor.

10.9. Post-study AEs

A post-study AE is defined as any event that occurs outside of the AE detection period defined in Section 10.3.

Investigators are not obligated to actively seek AEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the Investigator will promptly notify Arrowhead.

10.10. SAEs Related to Study Participation

An SAE considered related to study participation (e.g., procedures, invasive tests, a change in existing therapy), even if it occurs during the pre- or post-treatment period, will be reported promptly (refer Section 10.7).

11. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Statistical analyses and descriptive summaries will be presented for primary, secondary and exploratory endpoints using appropriate methods. A detailed statistical analysis plan (SAP) will be prepared and finalized prior to submission of the initial protocol to regulatory authorities prior to database lock. Descriptive statistics will be presented for all analyses unless otherwise specified. For continuous variables, data will be presented as number (n), mean, median, standard deviation, minimum, and maximum. Discrete variables will be presented as frequencies and proportions or percent.

11.1. Study Populations

Four study populations will be defined and evaluated in this study.

- Safety Population: All patients who receive at least one dose of study drug. The Safety Population will be used for safety analyses.
- Full Analysis Set (FAS): All patients 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) population: All FAS patients who did not violate the protocol in a substantial manner, such determination to be made prior to database lock.

11.2. Sample Size Considerations

There were no formal sample size calculations made in this open-label exploratory study.

11.3. Screening Data

Demographics will be tabulated by participant and summarized. Eligibility assessments at baseline, including medical/surgical history data and physical examination data (including height and weight), will be listed for each participant.

11.4. Safety/Tolerability Data

All safety analyses will be performed using the Safety Population. In general, safety analyses will be performed, and the results summarized by cohort. All safety summaries will be accompanied by patient listings. Baseline safety assessments will be compared with measurements recorded post-baseline.

- Treatment-emergent AEs will be summarized using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) by SOC and Preferred Term (PT), classified from verbatim terms. The incidence and percentage of participants with at least 1 occurrence of a PT will be included, per the most severe grade using a 3-point scale (mild, moderate, severe). The number of events per Preferred Term will also be

summarized. Causality (relationship to study treatment) will be summarized separately. The incidence and frequency of AEs, SAEs, related AEs, related SAEs, and AEs leading to withdrawal, dose modification, or treatment discontinuation will be summarized by dose according to SOC and PT.

- AEs will also be summarized in listings. The duration of AEs will be determined and included in listings, along with the action taken and outcome.
- The incidence of laboratory abnormalities will be summarized.
- Vital sign measurements will be summarized at each scheduled time point using descriptive statistics.
- Physical examination findings will be summarized by time point and presented in participant listings.
- Clinically significant changes on ECG and changes in spirometry (including VC, FVC, FEV_1), and DLCO will be summarized.
- Pregnancy test/FSH results will be summarized separately by time point.
- 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 will be summarized using Kaplan Meier estimates.
- The percentage of patients experiencing an ISR (see definition of ISR in protocol) will be summarized using descriptive statistics.
- Number and severity of COPD exacerbations based on GOLD criteria will be evaluated as an AE of special interest.

11.5. Immunogenicity Data

The number and percentage of patients who are ADA positive at baseline and at any post-baseline visit will be summarized. A listing of patients with positive ADA assay results will be provided.

11.6. Pharmacodynamic Data

AAT Levels: The whole blood collected for PD analysis following multiple doses of fazirsiran will undergo analysis for alpha-1 antitrypsin levels using both a Z-AAT specific assay and a clinical assay for total AAT. Results, including depth of knockdown as reported by percent change from baseline will be analyzed and summarized.

FibroScan®: Non-invasive imaging using FibroScan® will be completed pre-dose and post-dose per the SOA in a standardized fashion. Percent change in quantitative measure of liver stiffness from pre-dose to post-dose will be analyzed and summarized.

Liver Biopsy Assessments: Liver biopsy will be completed pre-dose and post-dose per the SOA or early termination. Primary, Secondary and exploratory endpoints will be based on comparison of pre-dose biopsy versus end of study biopsy unless otherwise specified and between cohort comparison conducted. Biopsy sample will be taken, prepped and stored in a standardized manner with biopsy. Histologic/IHC reads being completed by an independent central pathologist. Percent change in intra-hepatic Z-AAT, changes in PAS/D+ globules (size and number), change in a liver disease severity grading scale, mRNA, changes in Metavir fibrosis scale, fibrosis gene expression levels and Liver collagen and iron content using biomarkers, special stains and imaging [Masson's Trichrome, Sirius Red, Iron] (if scientifically feasible and sufficient sample available) from pre-dose to post-dose sample will be analyzed and summarized by cohort and between cohorts. A local reader at each site will be used during Screening to identify and exclude patients with pre-dose liver cirrhosis.

11.7. Analysis Methods

Demographic, PD and safety parameters will be summarized using descriptive statistics (n, mean, SD, % coefficient of variation (CV), geometric mean, geometric %CV, minimum, median, and maximum for continuous parameters; frequency and percentage for categorical parameters).

Detailed statistical considerations, such as biopsy derived measures analysis methods, missing data handling, study population definitions, and other important analysis issues will be described in a separate SAP. The SAP will be finalized prior to database lock.

Exploratory Analyses

The exploratory analyses are designed to investigate the association between treatment with fazirsiran and various biomarkers, liver proteins, gene and mRNA expression, FibroScan. These analyses will be exploratory, and data driven.

11.8. Data Recording and Quality Control

Source documents must be maintained for each participant in the study, consisting of all demographic and medical information, including clinical laboratory data, etc. A copy of the signed informed consent form must be retained. All information on the eCRFs must be traceable to these source documents in the participant's file.

Data recorded in all participants' eCRFs will be subjected to a quality control review.

12. STUDY APPROVAL AND CONDUCT

The following conditions will be met.

12.1. Regulatory Approval

The requirements for the conduct of clinical trials in accordance with local applicable regulations will be met before commencement of this study.

12.2. Ethics Committee (EC) Approval

Prior to initiation of the study, written EC approval of the Protocol and Informed Consent Forms, based on the principles of ICH cGCP procedures, will be received. A copy of the signed and dated letter of approval will be provided to the clinical site and Arrowhead Pharmaceuticals, Inc. prior to study commencement. Any written information and/or advertisements to be used for volunteer recruitment will be approved by the EC prior to use. A list of the EC voting members, their titles or occupations, Federalwide Assurance number (where applicable) and their institutional affiliations will be requested before study initiation.

Protocol modifications that may impact subject safety or the validity of the study will be approved by the EC, following written agreement from the Sponsor.

12.3. Ethical Considerations

This study will be carried out per the Declaration of Helsinki 1964, as modified by the 64th World Medical Assembly, Fortaleza, Brazil, October 2013, the Notes for Guidance on Good Clinical Practice (cGCP) (2000) (CPMP/ICH/135/95), and the Principles of the ICH cGCP. The protocol will be submitted for approval to the EC, and written approval obtained before patients are enrolled. The composition of the EC will also be provided to the Sponsor. If approval is suspended or terminated by the EC, the Investigator will notify the Sponsor immediately

Where applicable, the clinical site and Arrowhead Pharmaceuticals, Inc. agree to abide by the local compensation guidelines for injury resulting from participating in a company-sponsored research project. Compensation will only be provided on the understanding that the provision of compensation does not amount to an admission of legal liability and is subject to the proposed recipient signing a full and complete release of the company from all claims, damages and costs.

12.4. Written Informed Consent

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements. Study participation includes all screening procedures, as well as any wash-out of excluded medications.

It is the responsibility of the Investigator (or medically qualified designee) to obtain a written informed consent from everyone participating in this study after adequate explanation of the

aims, methods, objectives, and potential hazards of the study. The Investigator (or medically qualified designee) must also explain to the patients that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a written consent will be provided by the Investigator or by Arrowhead Pharmaceuticals, Inc.

For this study, each eligible participant will be required to provide written informed consent before participation in the study.

All eligible participants will have the study explained by the Investigator or designee. They will receive a full explanation, in lay terms, of the aims of the study, the discomforts, risks and benefits in taking part as well as of insurance and other procedures for compensation in case of injury. It will be explained that the study is for research purposes only and is not expected to provide any therapeutic benefit to the individual. It will be pointed out that they can withdraw from the study at any time without prejudice. Each participant will acknowledge receipt of this information by giving written informed consent for participation in the study. The volunteer will be given a copy of the signed Informed Consent Form to retain.

Patients will undergo reconsent in the period between the last dose in either Cohort 1, 1b, or 2 and before initiating participation in the treatment extension periods.

12.5. Emergency Contact with Principal Investigator

Suitable arrangements will be made for participants to contact the Investigator or medically trained designee in the event of an emergency.

12.6. Notification of General Practitioner

It is the responsibility of the PI or designee, to notify, where applicable, with the consent of the participant, the general practitioner of the subject's participation in the trial, by sending a letter stating the nature of the trial, treatments, expected benefits or adverse events and concomitant drugs to be avoided.

12.7. Clinical Laboratory Certification and Reference Ranges

Before the initiation of this study, the PI, or designee, will obtain a copy of the certification form, with certification number and expiration date for all clinical laboratories (excluding central laboratories) used in the study. Reference ranges for each clinical laboratory test used in this study will be obtained from the appropriate laboratory, which will perform the test for the study.

12.8. Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. The PI will conduct the study in compliance with the approved protocol and will not implement any deviation from or changes to the protocol without prior agreement by the Sponsor and review and documented approval from

the regulatory authorities and IRB/EC of an amendment, except where necessary to eliminate an immediate hazard to study patients.

Deviations may result from the action or inaction of the participant, PI, or site staff. Examples of deviations include, but are not limited to:

- Failure to adhere to study exclusion and inclusion criteria
- Failure to comply with dispensing or dosing requirements
- Use of medications, food, drink, herbal remedies, or supplements that are specifically prohibited in the protocol
- Missed or out-of-window visits
- Drug dosing not administered within the time frame specified in the protocol
- Failure to adhere to test requirements, including vital signs, laboratory tests, physical examinations, medical history, etc. – either tests not done, incorrect tests done, or not done within the time frame specified in the protocol
- Procedural deviations such as incorrect storage of study drug, failure to update the ICF when new risks become known, failure to obtain EC approvals for the protocol and ICF revisions

Protocol deviations impacting subject safety or eligibility will be reported to the Sponsor or CRO within 2 business days of occurrence and to the EC/competent regulatory authority per local regulatory requirements.

The Investigator is responsible for ensuring that any known protocol deviations are recorded and reported as agreed. The nature and reasons for protocol deviations will be recorded in each participant's CRF.

12.9. Termination of the Study

The Sponsor reserves the right to discontinue the trial at any time. Reasons will be provided in the event of this happening. The Investigator reserves the right to discontinue the study for safety reasons at any time in collaboration with the Sponsor.

13. STUDY ADMINISTRATION

13.1. Study Monitoring

Arrowhead Pharmaceuticals, Inc. is responsible for assuring the proper conduct of the study about protocol adherence and validity of the data recorded on the CRFs. Participant confidentiality will be maintained.

In accordance with applicable regulations, cGCP, and Arrowhead Pharmaceuticals, Inc. procedures, Arrowhead Pharmaceuticals, Inc. will be responsible for assigning a study monitor (CRA) who will contact the site to organize a visit prior to participant enrolment to review the protocol and data collection procedures with site staff. In addition, the assigned study monitor will periodically contact the site, including conducting on-site visits. The extent, nature and frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrolment rate.

During these site visits, the study monitor will:

- Check the progress of the study.
- Review study data collected.
- Conduct source document verification.
- Identify any issues and address their resolution.
- Check investigational product accountability
- Review blood and urine samples and ensure they are labeled and stored correctly.

This will be done to verify that the:

- Data are authentic, accurate and complete.
- Safety and rights of participants are being protected.
- Study is conducted in accordance with the currently approved protocol (and any amendments), cGCP and all applicable regulatory requirements.

The PI agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

At study closure, a study monitor will conduct the following activities in conjunction with the PI or site staff as appropriate:

- Return of all study data to Arrowhead Pharmaceuticals, Inc.

- Data queries.
- Accountability, reconciliation and arrangements for unused investigational product(s).
- Inventory and final disposition (e.g., destruction, shipping to repository, etc.).
- Review of site study records for completeness.

13.2. Quality Assurance

To ensure compliance with cGCP and all applicable regulatory requirements, Arrowhead Pharmaceuticals, Inc. may conduct a quality assurance audit of the study site. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the PI and clinical site agree to notify Sponsor as soon as possible following awareness of an impending regulatory inspection. The PI and clinical site agree to allow the auditor/inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

13.3. Records Retention

Following closure of the study, the PI must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection) and whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems and staff. When permitted by local laws/regulations or institutional policy, some of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The PI must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the PI must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

Arrowhead Pharmaceuticals, Inc. will inform the PI of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Arrowhead Pharmaceuticals, Inc. standards/procedures; otherwise, the retention period will default to 15 years.

The material to be stored shall include, but is not limited to, the following:

- Signed and dated copy of the final study protocol and any amendments.

- Signed and dated letter of IRB/EC approval, letter of constitution of the IRB/EC and copies of any other correspondence relevant to the study with the IBR/EC or regulatory authorities.
- The IRB/EC approved Informed Consent Form.
- Current *curriculum vitae* (signed and dated) of the Principal Investigator and co-workers with major responsibilities in the trial.
- Site Signature and Delegation of Responsibility Log
- FDA Form 1572 (where applicable)
- Financial Disclosure Form(s)
- Blank CRF/eCRF.
- Signed participant informed consent forms.
- Laboratory reference ranges (signed and dated).
- The completed CTN Application Form (where applicable).
- The Final Study Report.
- Clinical raw data including the Source Data Forms, all clinical laboratory report forms, subject CRFs, drug accountability forms, and dispensing records, etc.

14. INFORMATION DISCLOSURE AND INVENTIONS

14.1. Ownership

[redacted]

14.2. Confidentiality

[redacted]

14.3. Publication

[redacted]

[redacted]

15. REFERENCES

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APPENDIX 1. Elevated ALT Study Modification and Patient Discontinuation Rules

Treatment-Emergent ALT	Treatment-Emergent Total Bilirubin(TBL)	Liver Symptoms	Action
Normal baseline: ALT >5x ULN Elevated baseline: ALT >3x baseline or >300 U/L (whichever occurs first)	Normal	None	Repeat ALT, AST, ALP, TBL, in 2–3 days Follow-up for symptoms.
Normal baseline: ALT >8x ULN Elevated baseline: ALT >5x baseline or >500 U/L (whichever occurs first)	Normal	None	Interrupt study drug. Initiate close observation and workup for competing etiologies. (see below) Study drug can be restarted only if an alternative etiology is identified and liver enzymes return to baseline.
Normal baseline: ALT >3x ULN Elevated baseline: ALT >2x baseline or >200 U/L (whichever occurs first)	TBL >2x ULN	None	Interrupt study drug. Initiate close observation and workup for competing etiologies. Study drug can be restarted only if an alternative etiology is identified and liver enzymes return to baseline.
Normal baseline: ALT >3x ULN Elevated baseline: ALT >2x baseline or >200 U/L (whichever occurs first)	Normal or elevated	Symptoms of clinical hepatitis - severe fatigue, nausea, vomiting, right upper quadrant pain	Interrupt study drug. Initiate close observation and workup for competing etiologies. Study drug should not be restarted

Source: Adapted from Chalasani, Naga and Regev, Arie et al. Drug-Induced Liver Injury in Subjects with Preexisting Chronic Liver Disease in Drug Development: How to Identify and Manage? Gastroenterology, Volume 151, Issue 6, 1046 – 1051

Close observation for potential drug induced liver injury:

Within 72 hours, perform a complete history, physical, and liver biochemistries, including evaluation of:

- New or worsening signs and symptoms of clinical hepatitis such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia
- Concomitant medications, including acetaminophen, dietary supplements, herbal remedies, over-the-counter medications, recreational drug use, and special diets
- Alcohol consumption
- Exposure to environmental chemical agents
- Past medical history
- Complete review of systems
- Liver biochemistries including ALT, AST, alkaline phosphatase, total bilirubin, and INR.

Evaluate patients two or three times a week for signs and symptoms of clinical hepatitis and obtain liver biochemistries until biochemistries stabilize.

If biochemistries stabilize and the subject is asymptomatic, monitor liver biochemistries once a week until they return to baseline.

Patients who live far from study sites may be evaluated locally for history, physical exam, and laboratories, if the results are communicated promptly to the site investigator.

APPENDIX 2. Pulmonary Function Monitoring

Pulmonary function will be monitored closely throughout the AROAAT2002 study using spirometry, DLCO, weekly sponsor reviews and medical monitoring for pulmonary AEs.

- If a patient in the AROAAT2002 study experiences a decline of 10% or more in percent of predicted FEV_1 (must be confirmed on repeat within 30 days) from baseline with symptoms of chronic obstructive pulmonary disease (COPD) exacerbation,

- OR experiences a decline in percent of predicted FEV_1 by 10% (must be confirmed on repeat within 30 days) AND a decline in percent of predicted DLCO of at least 10%,

- OR a decline of percent of predicted FEV_1 of 20% or more (must be confirmed on repeat within 30 days), regardless of concurrent symptoms and regardless of any drop in percent of predicted DLCO,

they will be referred to a pulmonologist for possible initiation of augmentation therapy. Arrowhead will provide the therapy in any instance where the patient cannot access it through normal channels. Additionally, pulmonary monitoring visits for spirometry will be increased to approximately monthly.

If deemed necessary by the treating pulmonologist, AAT augmentation therapy may be initiated per locally approved package insert (typically weekly infusions at 60 mg/kg per dose) or equivalent for the duration of the AROAAT2002 study while the subject is on fazirsiran and for up to an additional six months after the subject's Z-AAT levels have returned to within 30% of their pre-dose Day 1 baseline AAT value OR until AAT levels have returned to within 30% of pre-dose Day 1 baseline and pulmonary function parameters (either DLCO or FEV_1) have stabilized (defined as two sequential measurements that are not declining) OR until cessation of augmentation therapy is deemed appropriate by treating pulmonologist. In the circumstance of patients in the study newly started on AAT augmentation therapy, measurement of AAT **may** increase in frequency from SOA to monthly or every two weeks. This measurement may be done with a Z-AAT specific assay or may require occasional AAT augmentation washout for measurement of endogenous production using the clinical AAT assay. In countries where augmentation is not available or not reimbursed, Sponsor will work to make therapy available as part of the AROAAT2002 clinical study.

APPENDIX 3. FIBROSIS STAGING SYSTEMS GUIDANCE

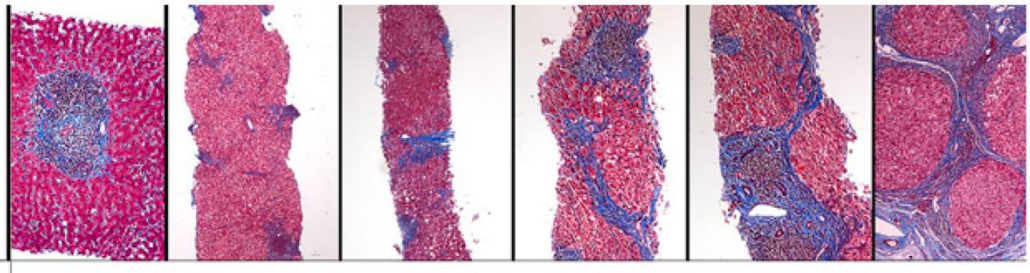
Guidance on the acceptable fibrosis scores based on different fibrosis staging systems for purposes of determining eligibility for the AROAAT2002 clinical trial.

The study relies on local pathologists for histological inclusion/exclusion evaluation. As such, Table 1 provides the numerical scores for commonly used fibrosis staging systems and highlights the scores accepted for liver fibrosis eligibility in AROAAT2002. The below figures and tables from published sources provide further reference for the staging system description and representative histological images. Sponsor recommends use of Ishak, Metavir or Scheuer Systems.

Table A1. Commonly used systems for fibrosis and general numerical comparison (yellow highlight represents stages eligible AROAAT2002 study)

Ishak	Metavir	Kleiner	Scheuer	Batts and Ludwig	2002 STUDY ELLIGIBILITY
0	0	0	0	0	NO
1	1	1a	1	1	YES
		1b			
2	2	1c	2	2	YES
3		2			YES
4	3	3	3	3	YES
5					YES
6	4	4	4	4	NO

Figure A1. Illustrative numerical comparison for common fibrosis staging (Fiel, MI. *Clin Liver Dis.* 14 [2010] 555-575)



Staging system						
Ishak	1	2	3	4	5	6
METAVIR	1	2	2	3	3	4
Scheuer	1	2	2	3	4	4
Batts & Ludwig	1	1	2	3	4	4

Table A2 Descriptive terms and corresponding fibrosis scores for common fibrosis staging systems (Fiel, MI. *Clin Liver Dis.* 14 [2010] 555-575)

Commonly used staging systems for fibrosis

Fibrosis Ishak System	Score
No fibrosis	0
Fibrous expansion of some portal areas, with or without short fibrous septa	1
Fibrous expansion of most portal areas, with or without short fibrous septa	2
Fibrous expansion of most portal areas with occasional portal-to-portal (P-P) bridging	3
Fibrous expansion of portal areas with marked P-P bridging and portal-to-central (P-C) bridging	4
Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis)	5
Cirrhosis, probable or definite	6
METAVIR System	**Stage**
No fibrosis	F0
Portal fibrosis without septa	F1
Portal fibrosis with few septa	F2
Numerous septa without cirrhosis	F3
Cirrhosis	F4
Scheuer System	**Stage**
No fibrosis	0
Enlarged, fibrotic portal tracts	1
Periportal or portal-portal septa, but intact architecture	2
Fibrosis with architectural distortion, but no obvious cirrhosis	3
Probable or definite cirrhosis	4
Batts and Ludwig	**Score**
No fibrosis	0
Portal fibrosis	1
Periportal fibrosis	2
Septal fibrosis	3
Cirrhosis	4

Data from Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. J Hepatol 1991;13(3):372–4; Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. Am J Surg Pathol1995;19(12):1409–17; Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22(6):696–9; Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR cooperative study group.

Table A3 Kleiner system descriptive terminology (*adapted* from Kleiner et al., *Hepatology* 41 [2005] 1313-1321.

Kleiner	Score
None	0
Perisinusoidal or periportal	1
Mild, zone 3, perisinusoidal	1a
Moderate, zone 3, perisinusoidal	1b
Portal/periportal	1c
Perisinusoidal and portal/periportal	2
Bridging fibrosis	3
Cirrhosis	4

Referenced protocol language

Inclusion 9:
Liver biopsy indicating Metavir F1- F3 (or equivalent on other grading scales) liver fibrosis based on local pathologist read within 6 months of consent. All patients will still require a liver biopsy during the screen period except for prior screened patients who now meet the fibrosis criteria as long as there is sufficient material for a baseline assessment.

Exclusion 25:
Diagnosis of F4 (Metavir) or similar grading scale equivalent indicating definitive cirrhosis on pre-dose liver biopsy completed as part of the AROAAT2002 study based on local pathologist read or based on historical liver biopsy (last 6 months from consent) with a source verifiable pathologist read of definitive liver cirrhosis.

Signature Page for VV-CLIN-000135 v2.0

Approval	[redacted]
Approval	[redacted]
Approval	[redacted]

Signature Page for VV-CLIN-000135 v2.0

Clinical Trial Protocol Approval Form

Protocol Title/ID: A Pilot Open Label, Multi-dose, Phase 2 Study to Assess the Safety and Efficacy of Fazirsiran (TAK-999, ARO-AAT) in Patients with Alpha-1 Antitrypsin Deficiency Associated Liver Disease (AATD) / AROAAT2002

Protocol/Amendment Version: AROAAT2002 Global Protocol Amendment v7.0

Version Number/Date: Version 7.0, 21 July 2022

Country Template Version Number/Date: N/A

Approved by:

[redacted]

Clinical Development Medical Monitor: [redacted] Date

[redacted]

Clinical Operations Therapeutic Area Lead: [redacted] Date

[redacted]

Biostatistician: [redacted] Date