



# Alpha-1 Antitrypsin Deficiency FDA Workshop *RNAi Therapeutic Approach to AATD Liver Disease*

Sept. 16, 2019

# Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, enter into collaborations and achieve other projected milestones, rapid technological change in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

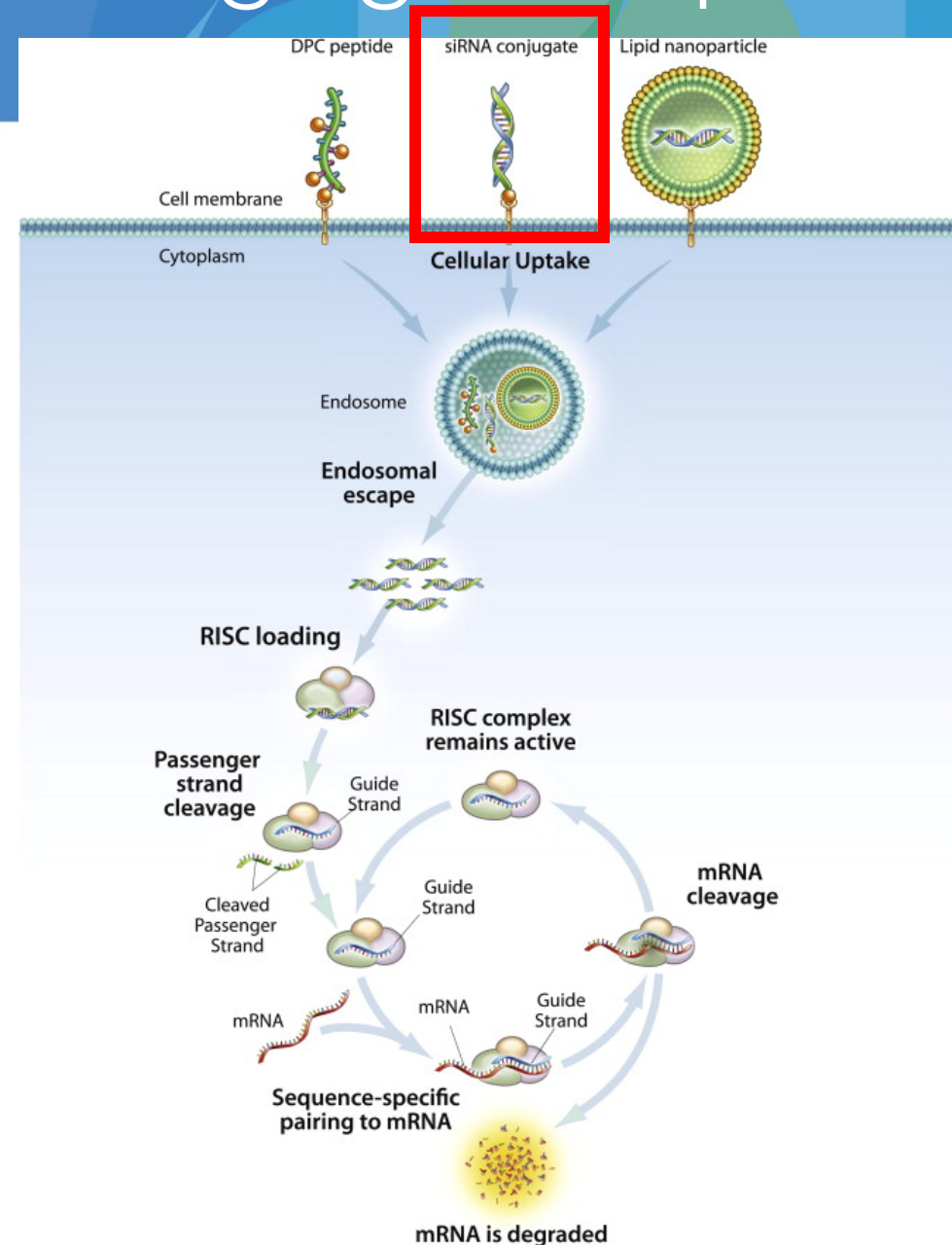
# Clinical Development Challenges in AATD Liver Disease

Developing drugs for alpha-1 liver disease is very complex with many challenges

Development Challenge	How Arrowhead is addressing
<ul style="list-style-type: none"><li>AATD is rare and liver disease in AATD is even more rare</li></ul>	<ul style="list-style-type: none"><li>Worked with U.S. regulators to adopt an adaptive clinical trial design allowing Phase 2 dose range finding to “seamlessly” feed into Phase 3</li></ul> <ol style="list-style-type: none"><li>Maximizes “value” of rare patients</li><li>Helps minimize time in development</li></ol>
<ul style="list-style-type: none"><li>Lack of clear understanding of disease progression</li></ul>	<ul style="list-style-type: none"><li>Conducting a retrospective natural history study in PiZZ patients with liver disease.</li></ul>
<ul style="list-style-type: none"><li>No well accepted efficacy surrogate</li></ul>	<ul style="list-style-type: none"><li>Development of a novel histological grading scale specific to AATD liver disease</li></ul>

# siRNA Gene Silencing: An Emerging Therapeutic Modality

- RNAi is a method of silencing gene targets and is an emerging therapeutic modality
- Relies on delivery of siRNA into the cytoplasm
  - Liposomes or ligand directed hepatocyte uptake via asialoglycoprotein receptor
- Stable siRNA molecules survive endosome, engage with RISC to silence mRNA
- Catalytic nature of siRNA leads to long duration of potent gene silencing

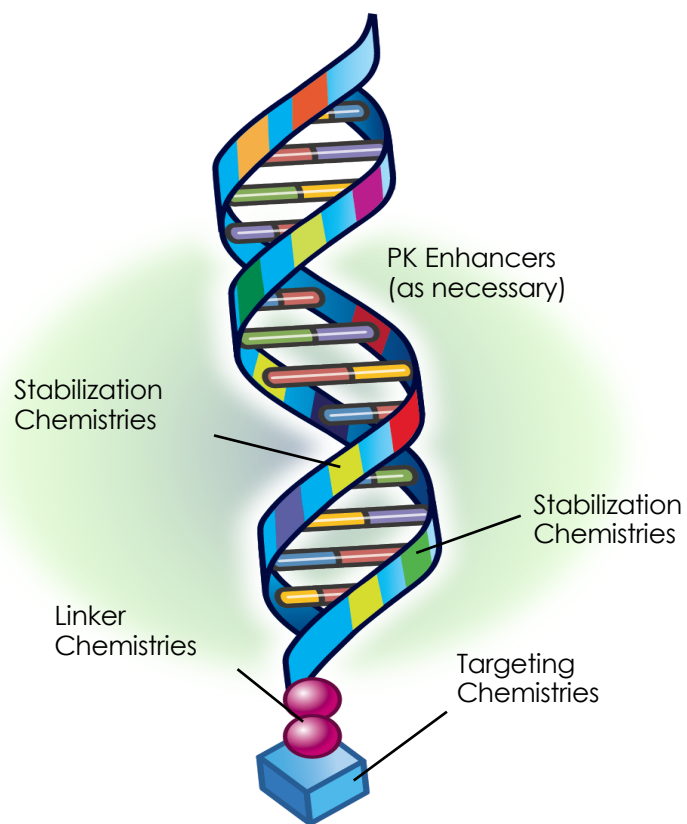


# siRNA Gene Silencing: A Maturing Therapeutic Approach

- May be ideal for:
  - Targets not addressable with small molecules or monoclonal antibodies
  - Where systemic exposure and off target effects may lead to unacceptable toxicity.
- One FDA approved product (patisiran for hereditary transthyretin mediated amyloidosis) utilizing liposomal intravenous delivery
- Multiple “GalNac” conjugates in late stage development

# ARO-AAT

## Targeted RNAi Molecule TRiM™ platform



ARO-AAT: Investigational product in development to address liver disease in AATD

Hepatocyte targeted RNAi molecule

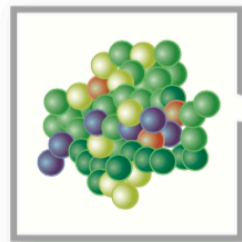
Specifically targets AAT mRNA

Silencing is hepatocyte specific

Designed to minimize off-target gene silencing

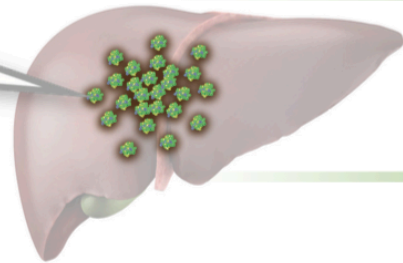
# Liver Disease in Alpha-1 Antitrypsin Deficiency

Alpha-1 Antitrypsin protein

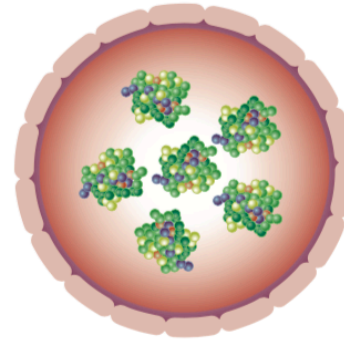


Normal AAT

Normal liver

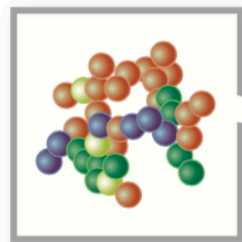


Normal secretion into the blood



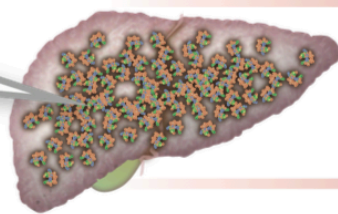
*Normal blood levels of normal protein protect lungs, no liver accumulation*

Misfolded Alpha-1 Antitrypsin protein



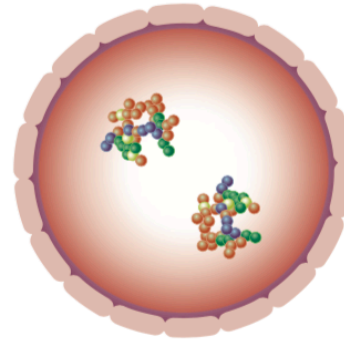
Abnormal AAT (Z-AAT)

Liver affected by AATD



Abnormal secretion into the blood

*High accumulation of misfolded Alpha-1 Antitrypsin protein leads to liver injury*



*Low blood levels of abnormal protein leaves lung susceptible to damage from inflammation caused by inhaled irritants or infection, accumulated protein injures liver*

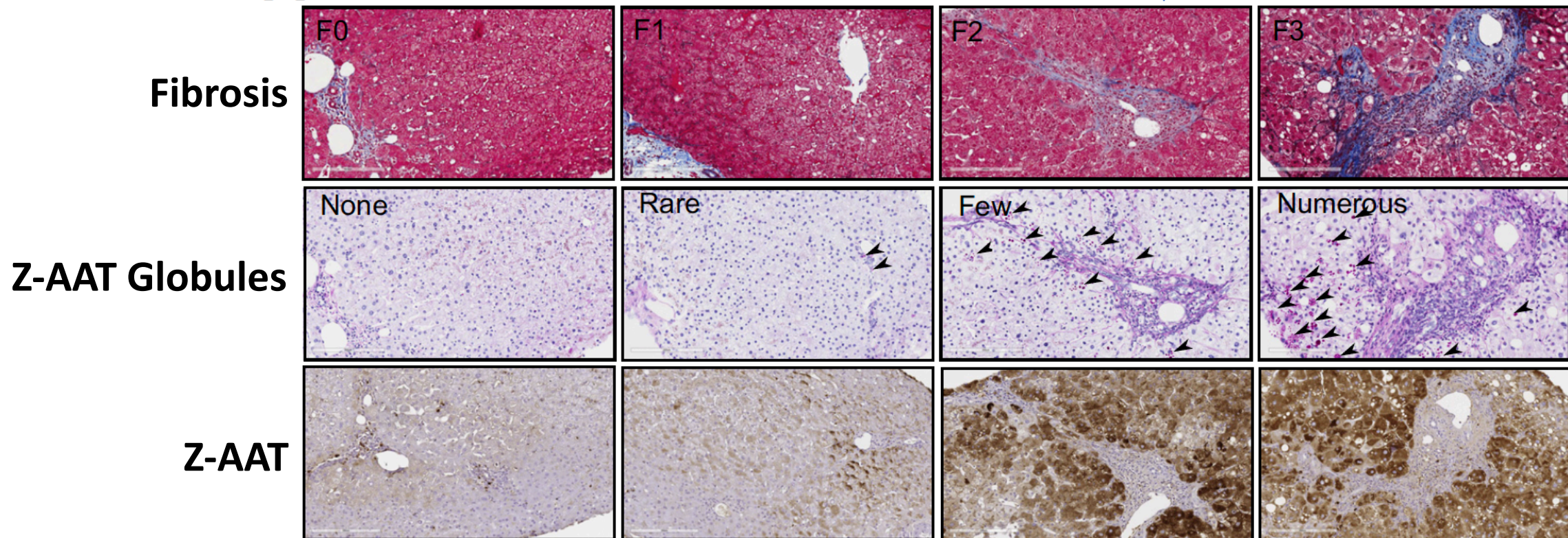
**No current treatment**

**Lung Disease Treated with AAT protein replacement therapy today**

# Underlying Fibrosis Found in Natural History Study

Clark et., *J. Hep.* 2018

- 94 ZZ Patients underwent a Biopsy
- 33 (35%) had what was considered significant ( $\geq$  F2) fibrosis



No PAS-D  
No Fibrosis



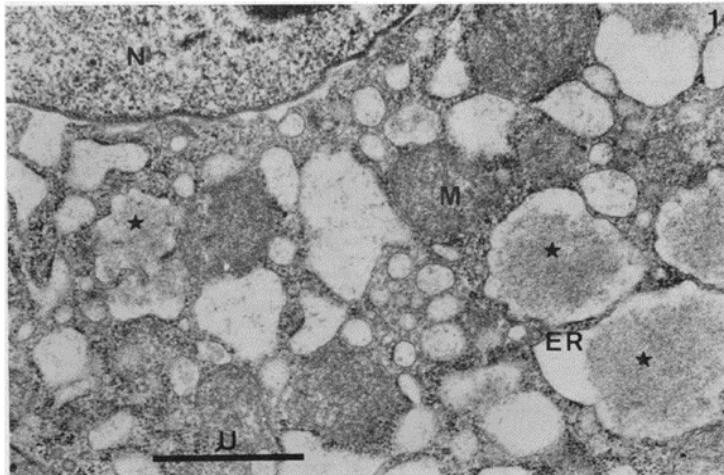
Abundant PAS-D  
Abundant Fibrosis



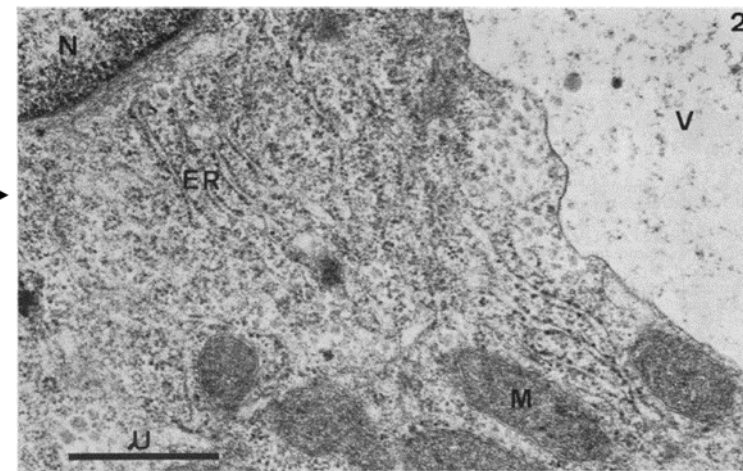
# ARO-AAT Therapeutic Rationale

- RNAi trigger designed to stop Z-AAT production by silencing AAT gene to:
  - Prevent accumulation of Z-AAT in liver
  - Allow clearance of accumulated Z-AAT protein
  - Prevent repeated cycles of cellular damage
  - Prevent/Reverse progression of liver fibrosis

**PiZZ phenotype (diseased)**



**Pi null phenotype (normal)**

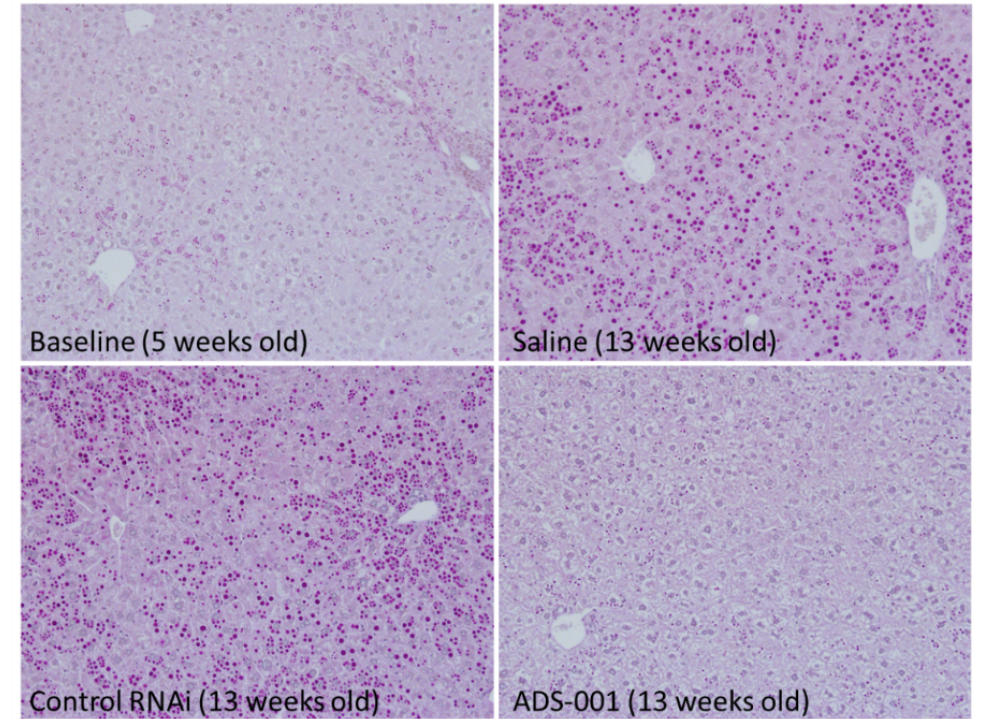
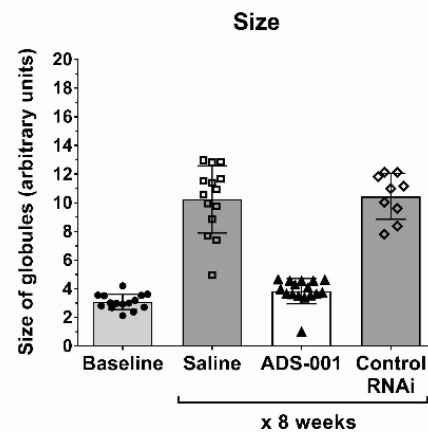
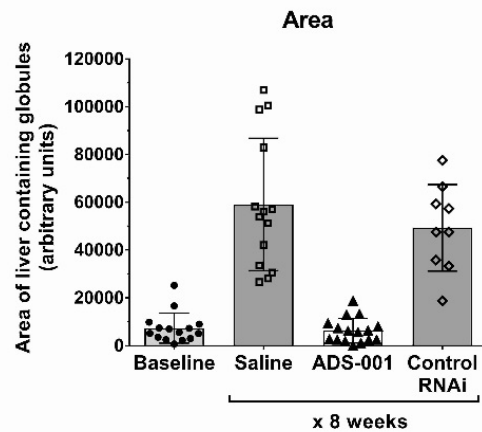
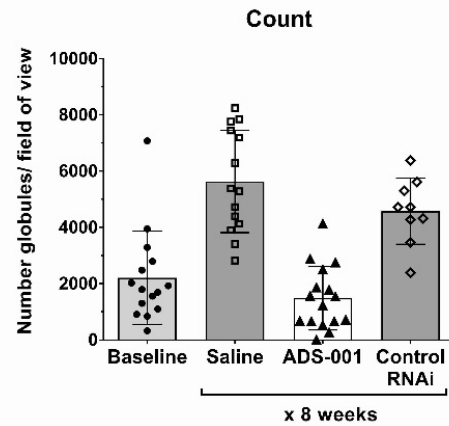


# Safety Considerations with this Approach

- While AATD is a storage disease in the liver, it is a deficiency disease relative to the lung.
  - Emphysema takes decades to develop in AATD patients
  - Null/null patients are thought to develop emphysema faster
  - While not creating true null/null plasma levels due to extra-hepatic production, RNAi will further reduce serum AAT levels and pulmonary risk is the key disease-specific toxicity to be assessed in clinical programs. Thus, finite therapy would be preferred, if feasible
- Attempts are made to exclude potential off-target gene silencing and normal GLP tox work is performed, unexpected toxicity in humans is possible.

# ARO-AAT: Prevents Liver Globule Accumulation

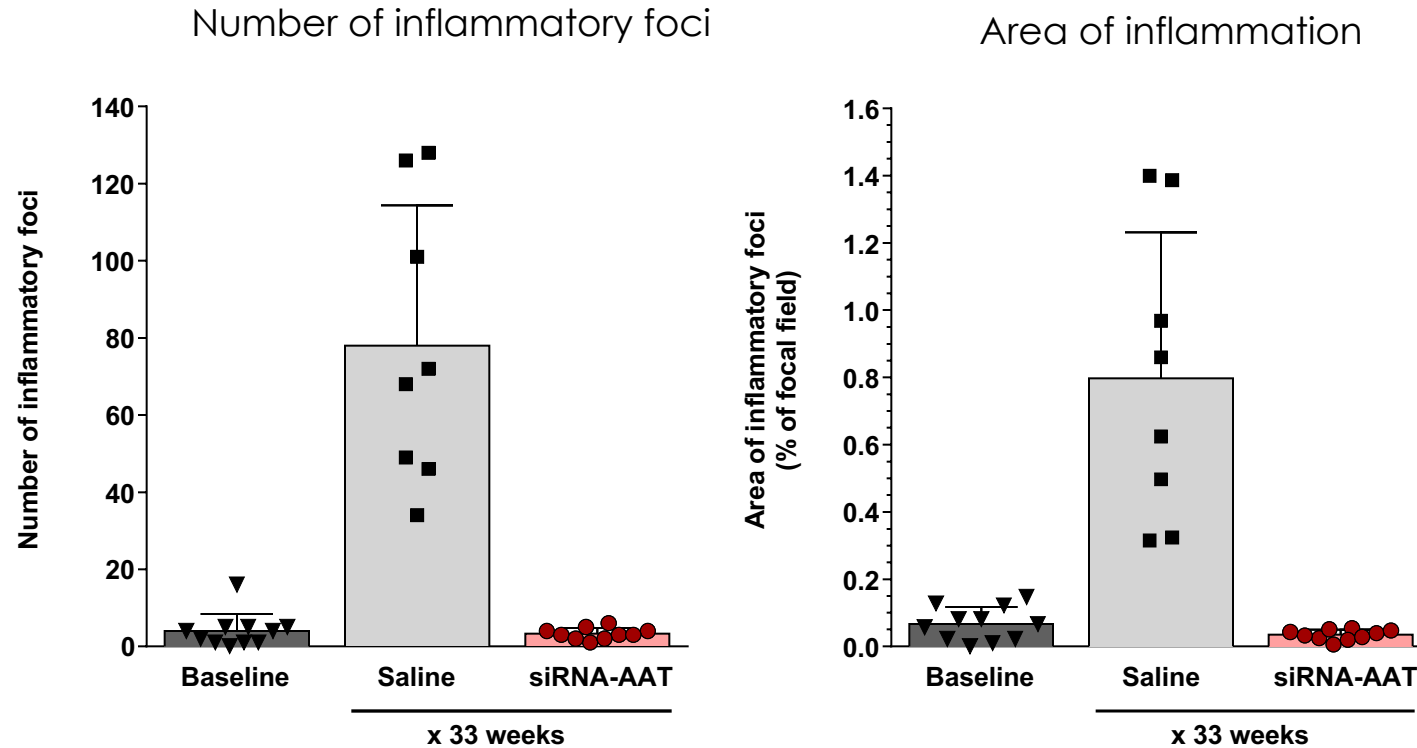
PiZ Transgenic mouse model



# siRNA Effect on Liver

PiZ Transgenic mouse model

Prevention of inflammation in the liver



ARC-AAT treatment prevented inflammation

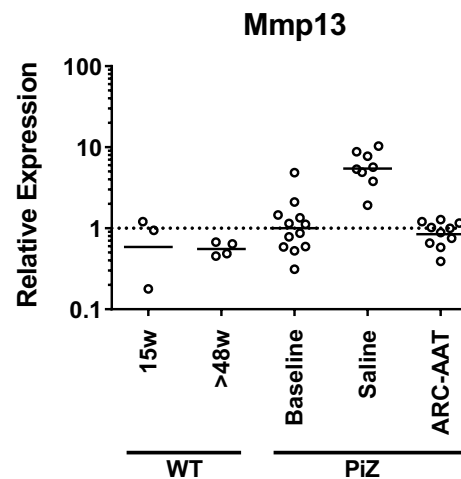
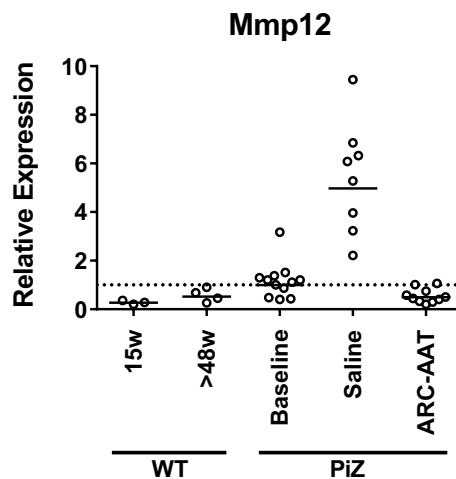
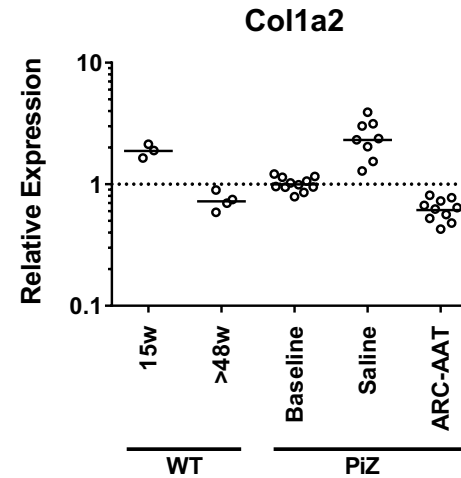
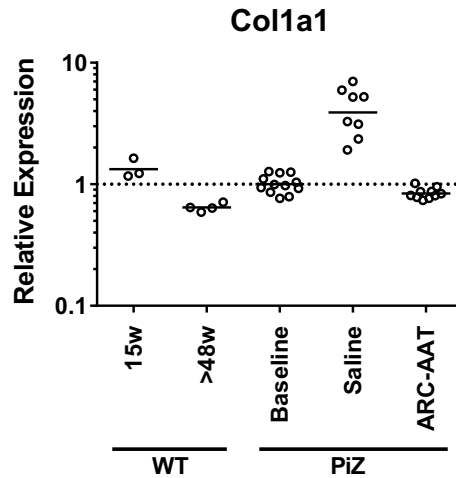
- Fewer inflammatory foci
- Reduced total area of inflammation

AASLD talk 2016

# siRNA Effect on Fibrosis Associated Gene Expression

Reduced gene expression associated with fibrosis in the liver

PiZ Transgenic mouse model



- Fibrosis gene expression increases with age in untreated (saline group) PiZ mice
- ARC-AAT prevents the increase in fibrosis gene expression

AASLD talk 2016

# ARO-AAT Phase 1 Study in Healthy Volunteers

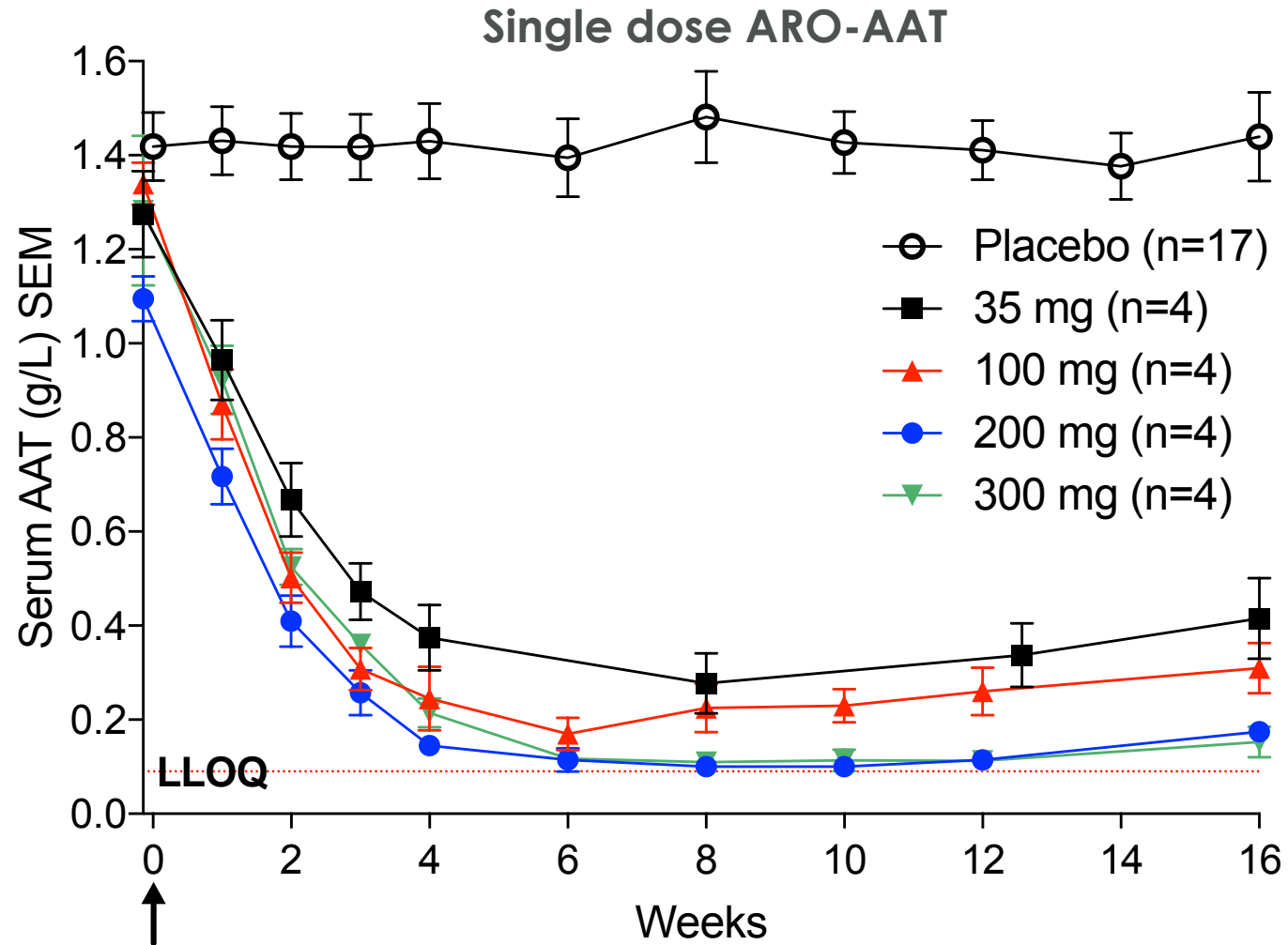
## OPEN LABEL

- 3 groups
  - **Single dose** of 100, 200 and 300 mg of ARO-AAT
  - 4 per cohort
- Assessments of safety, tolerability, depth and duration of AAT reductions after a single dose

## DOUBLE BLIND

- 4 treatment arms
  - 35, 100, 200 and 300 mg
  - 100, 200, 300 mg receive **3 monthly doses**
  - 4 active, 4 placebo
- Assessments of safety, tolerability, plasma levels of ARO-AAT, plasma AAT changes

# ARO-AAT Phase 1, NHV SAD/MAD Study



# ARO-AAT Phase 1: Summary Safety

## ARO-AAT Phase 1, NHV SAD/MAD study Safety Summary

- 45 NHVs received at least 1 dose (28 active, 17 placebo)
- No deaths, severe AEs or serious AEs reported
- Mild Local Injection Site Reaction (LISR) in 4% of ARO-AAT injections
  - LISR defined based on MedDRA preferred term for injection site AEs with duration of at least 48 hours
- No AEs secondary to platelet count declines, changes in renal function parameters or changes in markers of liver injury/function
  - 3 treatment emergent grade 1 ALT elevations, all returned to baseline by end of study, with max elevation < 2X ULN

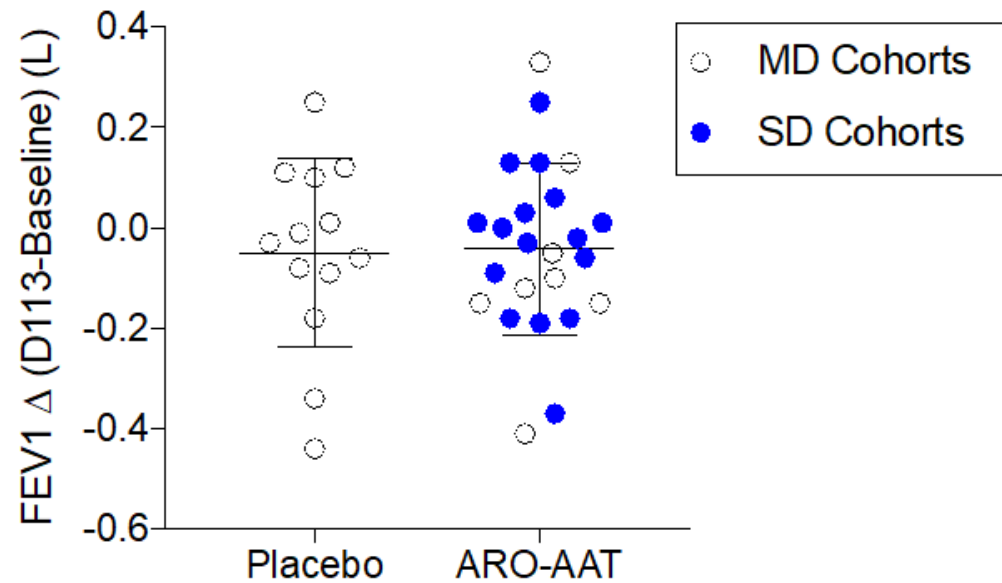


# Pulmonary Safety: Considerations and Inclusion Criteria

## ARO AAT1001 lung related I/E criteria

- Emphysema in AATD takes decades to develop, so not expecting to see pulmonary AEs in a relatively short study, nonetheless monitoring of lung function important in this NHV study.
- Required non-smoker, normal FEV1 (based on ATS-ERS guidelines) at baseline
- Normal serum AAT at baseline (above lower limit of normal range, 90 mg/dL)
- Conducted spirometry at multiple timepoints throughout study and during post-study follow up
- FEV1 decline of at least 200 mL from baseline was prespecified minimal important difference
- FEV1 is an effort dependent test, intra-subject variability can be a difficult issue during a short study

# FEV1 Summary Through Day 113/EOS

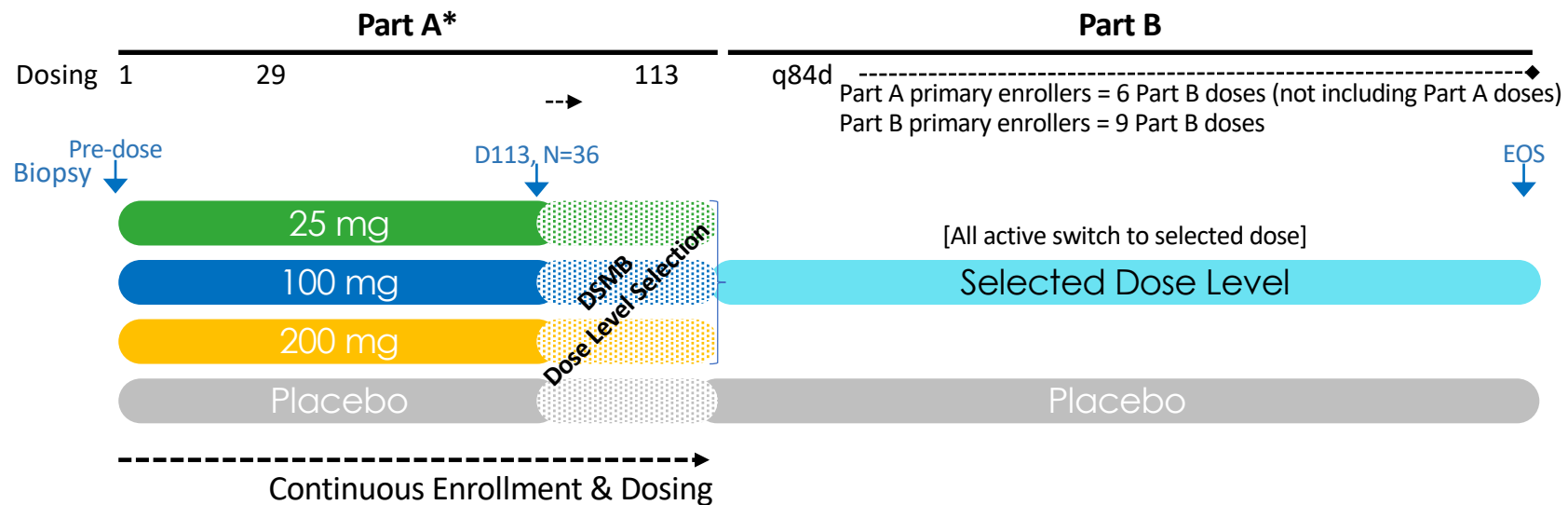


AASLD 2018

- No AEs of dyspnea or other symptoms consistent with lung parenchymal damage
- 3 AEs of FEV1 decline, 1 active (3.6%) v 2 placebo (11.8%). None with reported symptoms. 1 on active rebounded above baseline FEV1 in extended follow up with near max AAT KD
- Declines in FEV1 of at least 200 mL on D113: 2 (8.6%) active v 2 (15.4%) placebo
- Declines in FEV1 of at least 200 mL at any visit through D113: 6 (21%) active v 2 (11.7%) placebo
- No statistically significant difference (ANCOVA) between active versus placebo FEV1 changes (% predicted or mL) at any study visit.

# ARO AAT2001 Study Design

**N=120 total, Randomization = 2:1 (active:placebo)**



\* All patients enrolled prior to Part B dose selection will be randomized to Part A cohorts and receive at least 3 doses at the Part A dose level before switching to Part B dose level. Only 1<sup>st</sup> 36 will require D113 biopsy.

**Placebo patients will be rolled over to ARO-AAT at end of study**

# Key Questions to Answer in Phase 2/3 Adaptive Trial

- Phase 2
  - Dose response for hepatocyte Z-AAT knockdown in PiZZ AATD patients
  - Safety/tolerability (including pulmonary) of multi-dose treatment in PiZZ AATD patients
  - Best dose for maximizing AAT knockdown in context of safety/tolerability
  - Best dose selection by DSMB in consultation with FDA (sponsor remains blinded)
- Phase 3
  - Improvement in an AATD specific histological scale without worsening of fibrosis
  - Safety with special attention to pulmonary effects

# Summary

- RNAi consistently induces deep and prolonged reductions in serum AAT levels, likely due to hepatocyte gene silencing
- In NHVs, no clear association between AAT decline and adverse FEV1 changes or pulmonary AEs over a several month period
- While FEV1 declines as a measure of pulmonary toxicity were not expected in Phase 1, results from this study are reassuring, particularly if ARO-AAT can be used as a finite duration therapy (e.g. 2-3 years) to ameliorate Z-AAT liver accumulation
- More data is needed in an AATD patient population with longer treatment periods
- The AROAAT2001 study is the result of constructive collaboration with U.S. regulators to develop a novel clinical trial approach to AATD liver disease
- Study is open for enrollment and is the first study to evaluate the impact of gene silencing on AATD liver histology and pulmonary function



Thank you!

Alpha-1 Antitrypsin Deficiency  
FDA Workshop

*Gene Silencing Approach to AATD Liver Disease*