ARO-AAT: An Investigational Therapeutic for AATD Liver Disease

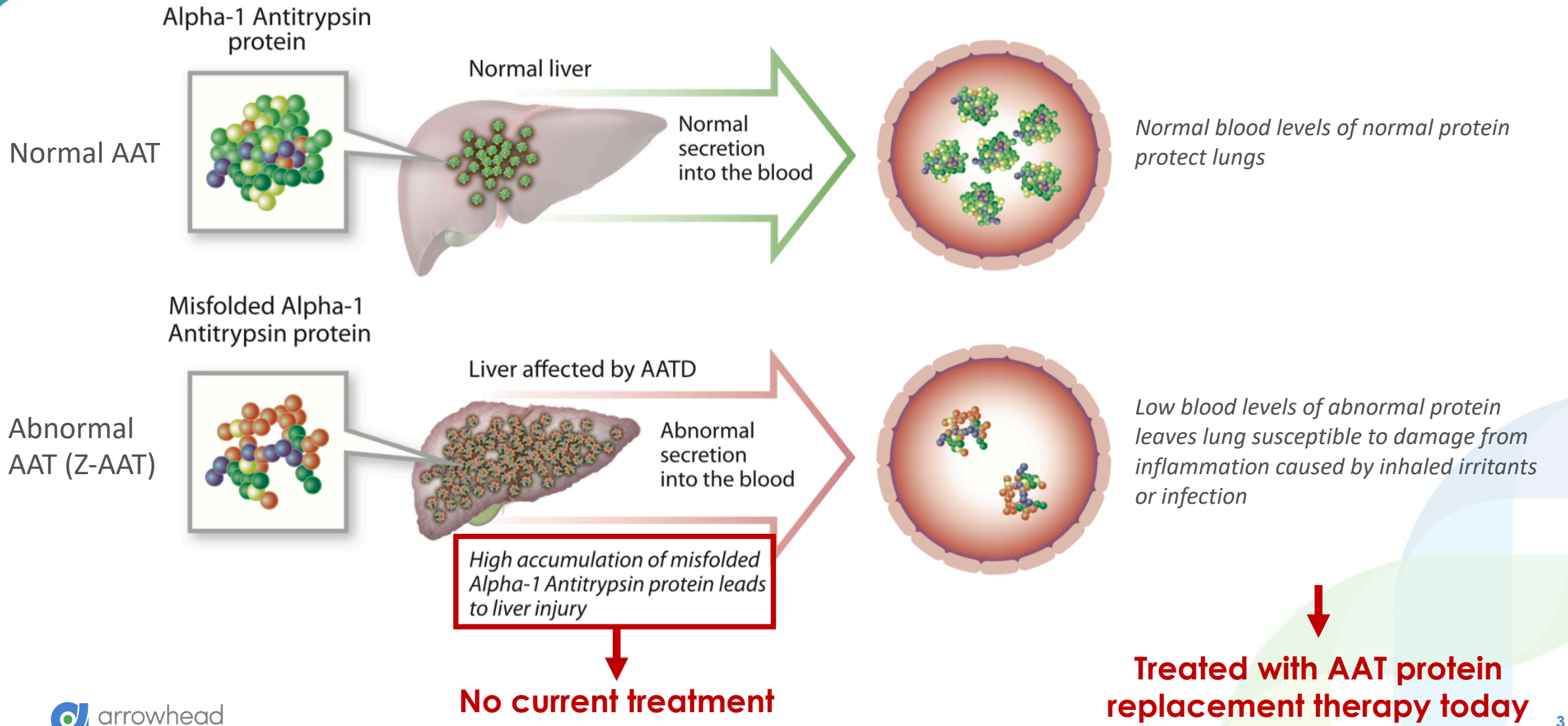
September 14, 2019

arrowhead pharmaceuticals

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.

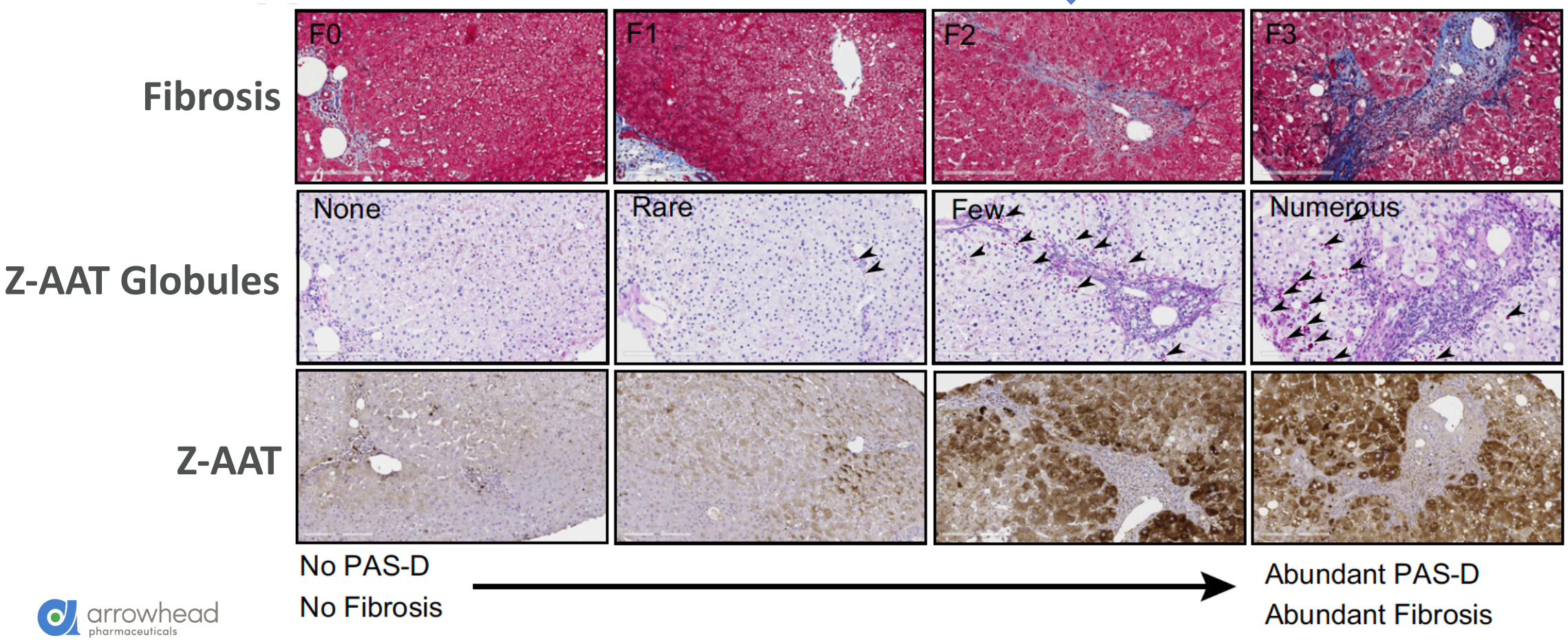
Alpha-1 Antitrypsin Deficiency



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 fibrosis

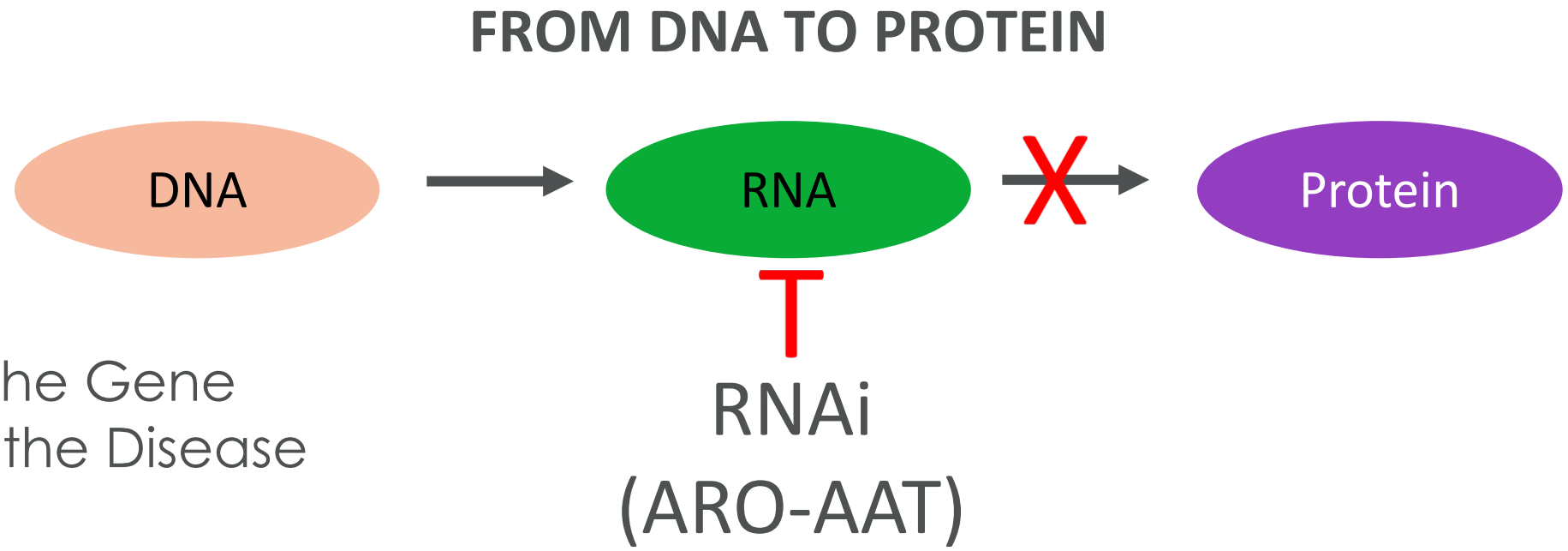


Why is Liver Injury Problematic?

Liver Functions:

- Removal of toxins
- Produces bile needed for digesting food and absorbing vitamins
- Stores nutrients (e.g. fats, sugars) for use as energy
- Synthesis of proteins important for:
  - Fighting infection
  - Clotting of blood

Arrowhead: RNAi-based therapeutics: *What is RNAi?*



RNAi = RNA interference

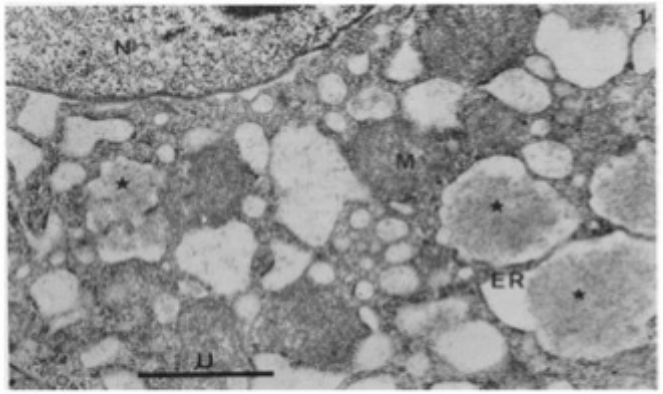
- RNAi silences gene expression so specific protein is not produced
- RNAi triggers can be designed and synthesized to target a specific protein
- Not gene therapy or gene editing which may actually modify the genome

ARO-AAT: Mechanism of Action

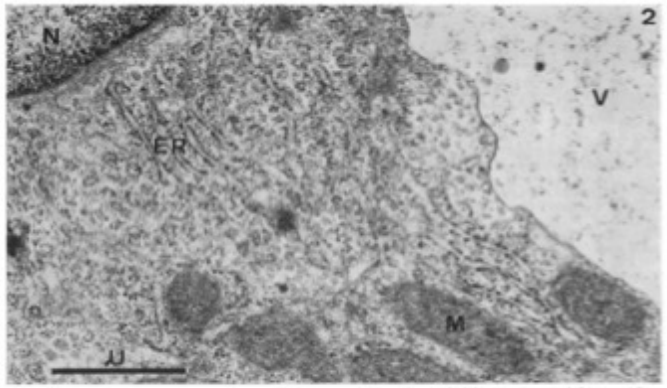
ARO-AAT designed to stop Z-AAT production by silencing AAT gene expression to:

- Prevent liver accumulation of Z-AAT
- Allow clearance of accumulated Z-AAT protein
- Prevent cycles of cellular damage
- Prevent/Reverse progression of liver fibrosis

PiZZ phenotype (diseased)



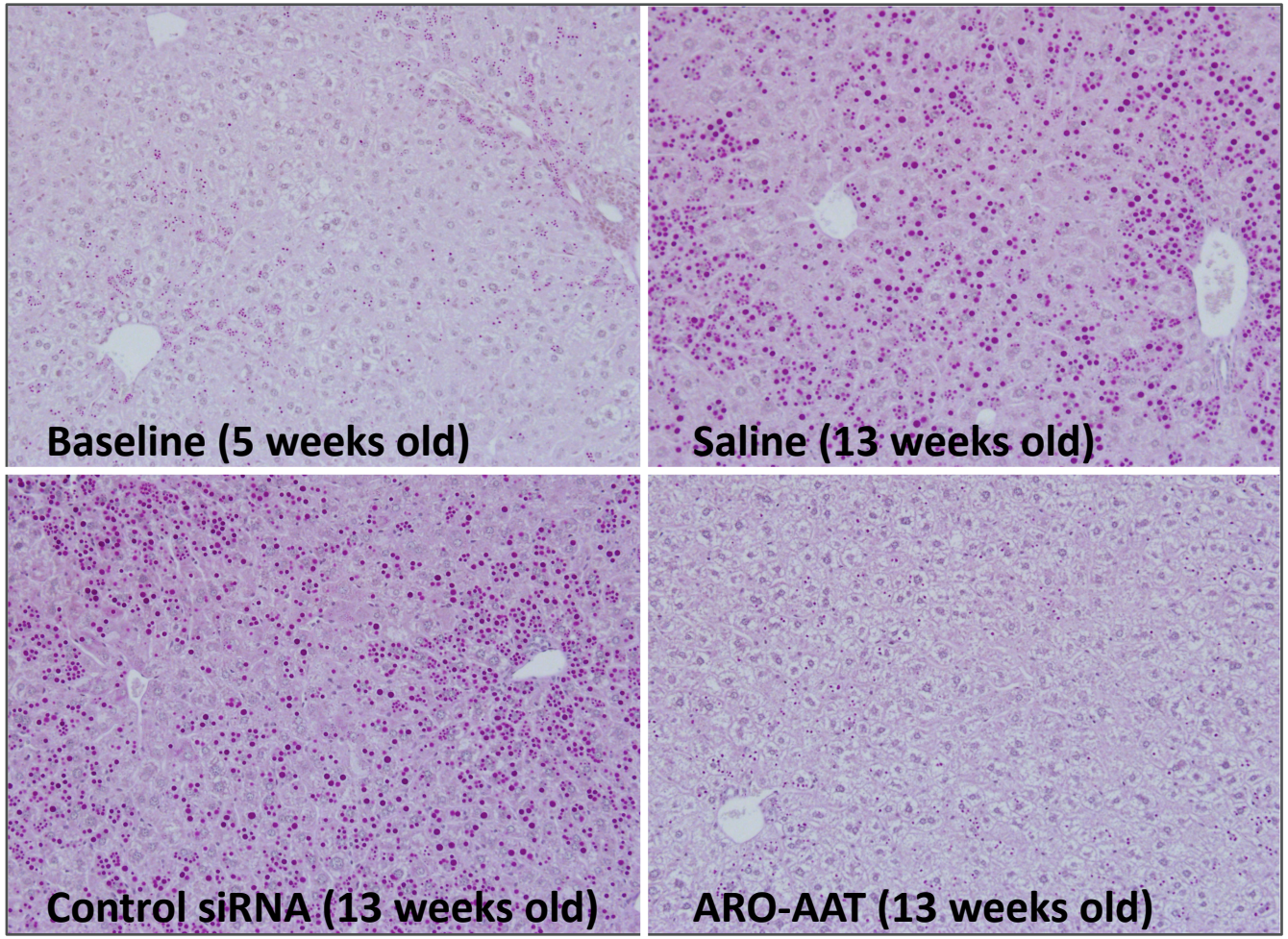
Pi null phenotype (normal liver)



Feldmann G et al., *Gut* 1975

ARO-AAT Reduces Z-AAT and Prevents Globule Accumulation in Young PiZ Mice

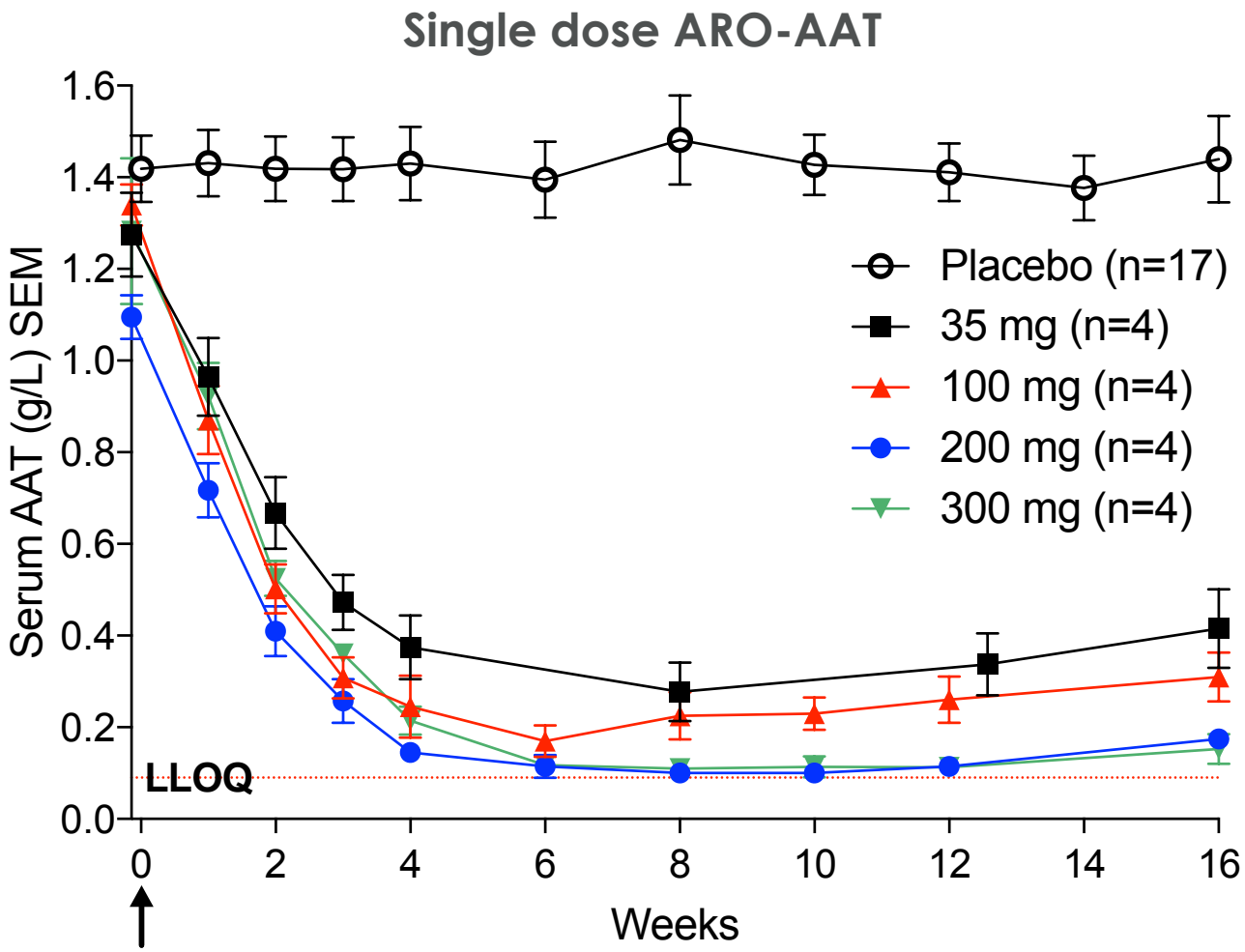
Subcutaneous Injection



AROAAT1001 Clinical Study in Healthy Volunteers

- **Subcutaneous Injection**
- Single and Multiple (x3) doses studied in Healthy Volunteers
  - Multiple doses = **monthly**
- Dose levels 35, 100, 200, 300 mg
- Assessments of safety, tolerability, pharmacokinetics (drug blood levels) depth and duration of serum AAT reductions
  - All cohorts being followed until serum AAT returns to normal or within 20% of baseline
- **Dosing completed**
- 45 total subjects enrolled (including one replacement: 28 active, 16 placebo)

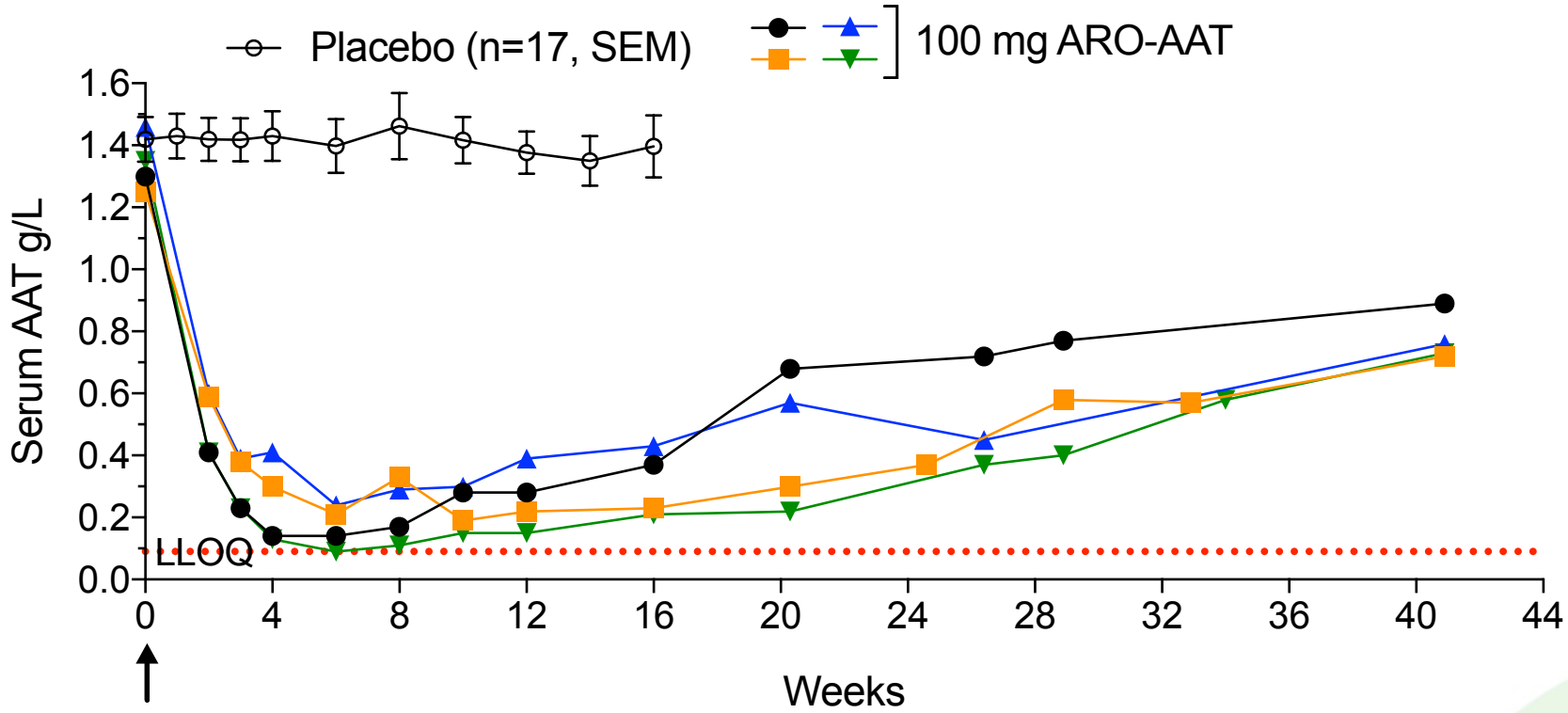
AROAAT1001 Serum AAT Dose-Response



Supports quarterly or less frequent dosing

AROAAT1001 Serum AAT Reduction Duration

Single dose ARO-AAT



Current Clinical Studies

AROAAT2001 SEQUOIA

- Phase 2/3 adaptive design study
- # of ZZ Patients planned=120
- **Location:** Multiple sites in **UK**, EU, US and Canada
- Duration: 2-year minimum treatment
- Subcutaneous injection every 3 months after 2nd dose
- Biopsy required
- Placebo controlled
- At end of study all placebo will have the option to receive active in an extension study
- Part A Objective: to select a dose level for Part B
- Part B Objective: To evaluate efficacy based on biopsy
- Status: Currently Enrolling

AROAAT2002

- Phase 2 study
- # of ZZ patients planned=12
- **Location: UK**, Germany, Austria
  - **Birmingham, Edinburgh, Cambridge**
- Duration: 6 to 24 month treatment
- Subcutaneous injection every 3 months after 2nd dose
- Biopsy required
- No Placebo
- Objective: To assess changes in liver disease activity scale based on biopsy
- Status: Expect to be recruiting by end of year (2019)

In Conclusion…….

- Liver Disease is the silent killer in AATD
- Thanks largely to the Alpha 1 Foundation and Physician/Research Community it is now coming out of the shadows
- ARO-AAT is a RNAi drug designed to halt liver production of AAT in the liver with infrequent, subcutaneous injection
- The SEQUOIA trial (AROAAT2001) is the first trial designed to potentially serve as a pivotal trial for approval
- For more information on ARO-AAT studies, please visit www.clinicaltrials.gov(enter key word: ARO-AAT) and/or speak to your physician