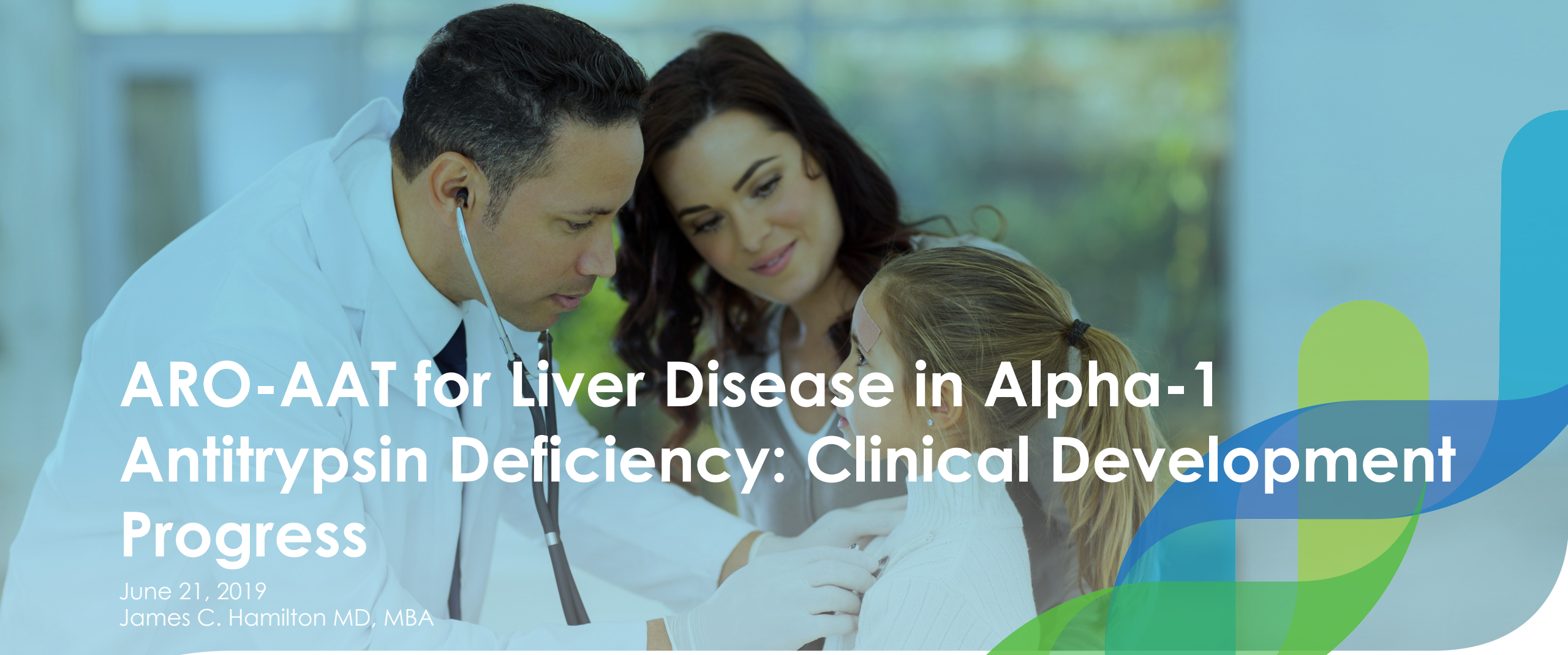

ARO-AAT for Liver Disease in Alpha-1 Antitrypsin Deficiency: Clinical Development Progress

June 21, 2019

James C. Hamilton MD, MBA

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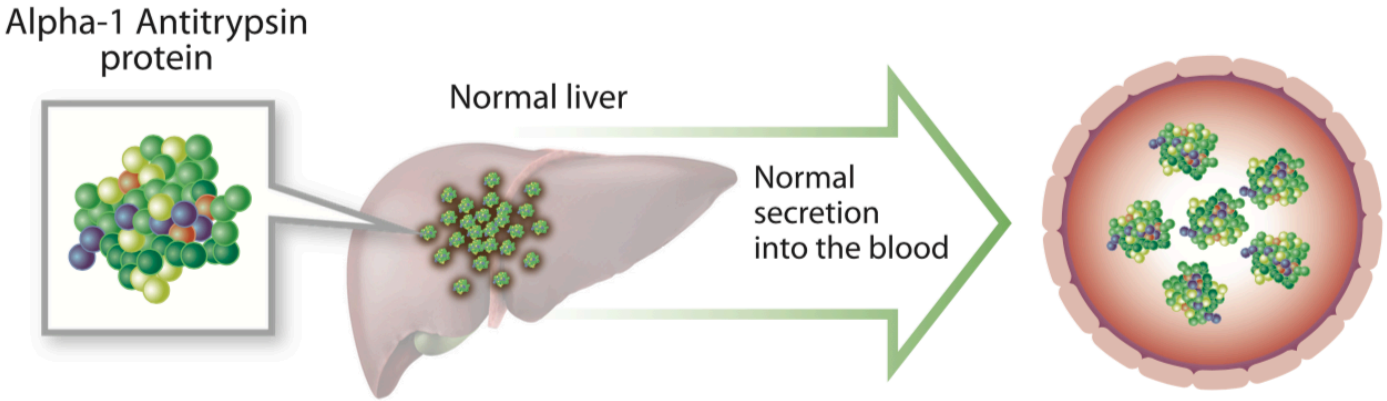
This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and 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.

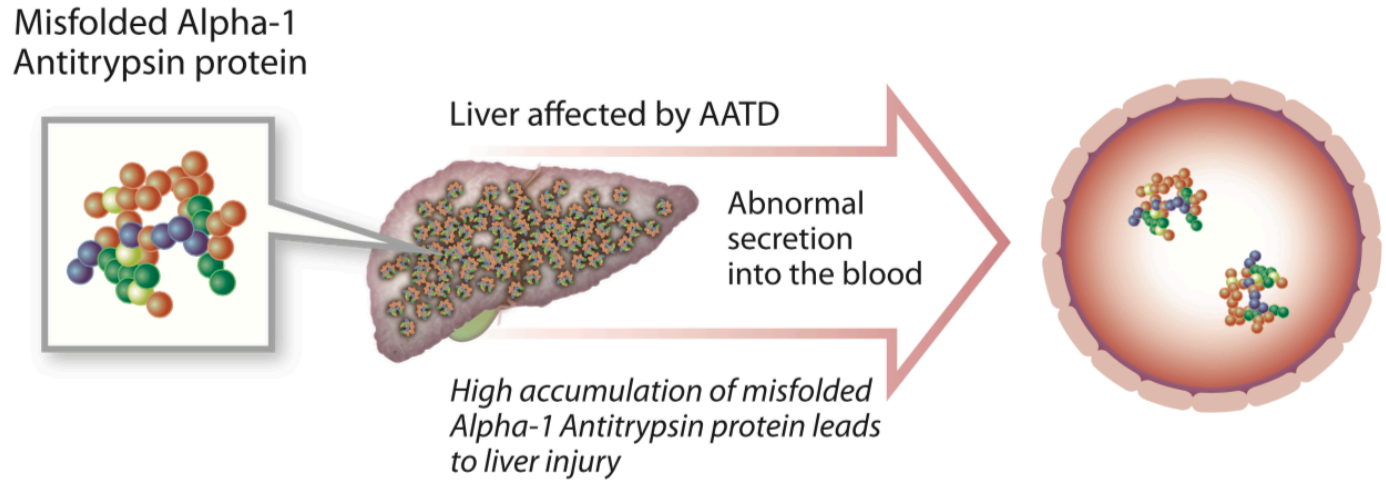
Alpha-1 Antitrypsin Deficiency

Normal AAT



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

Abnormal AAT (Z-AAT)



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

Treated with AAT protein replacement therapy today

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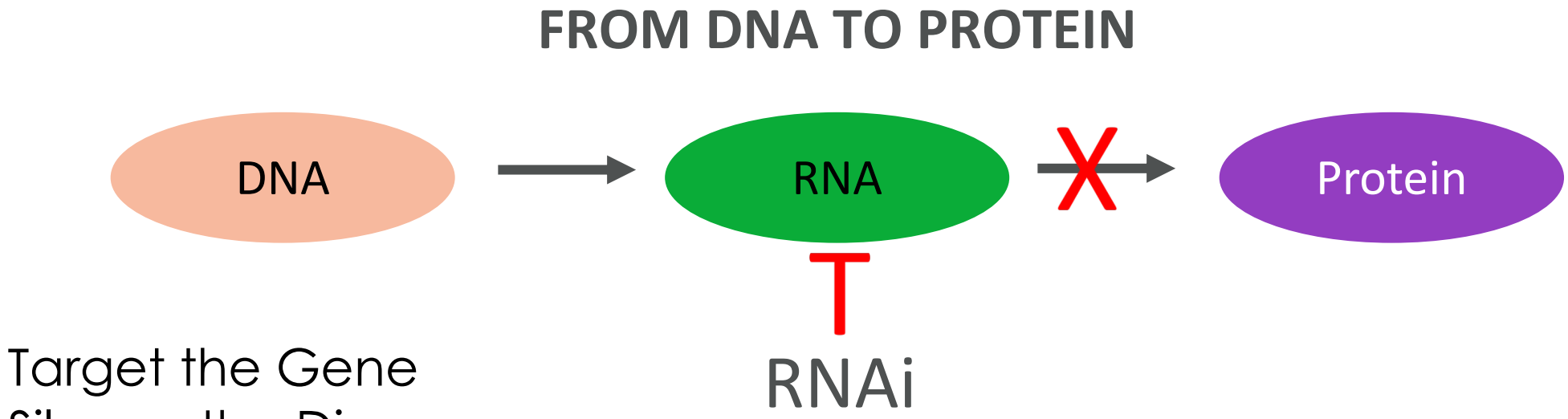
What is the Risk of Developing Liver Disease

Recent study on liver involvement in AATD (Clark et al., 2018)

- Evaluated 94 PiZZ AATD adult patients
- 35% demonstrated clinically significant (≥ F2) liver fibrosis based on biopsy
- Additionally, common medical conditions may further increase risk
  - Obesity
  - Hypertension
  - High cholesterol
  - Diabetes

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



RNAi = RNA interference

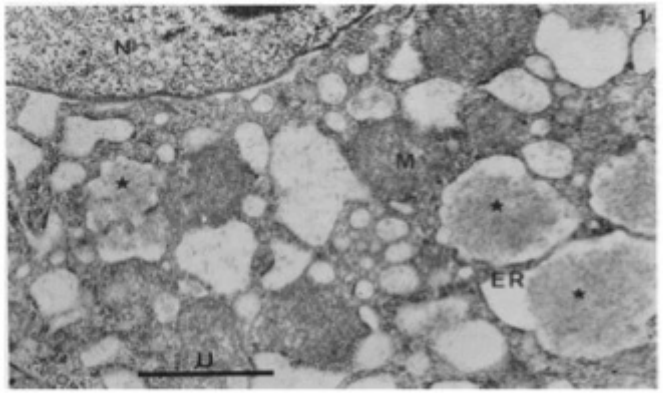
- Normally, genes (DNA) transcribed into RNA which are translated into proteins
- RNAi inhibits the mRNA in a manner that is specific for a single gene
- Not gene therapy or gene editing which may actually modify the genome

ARO-AAT: Mechanism of Action

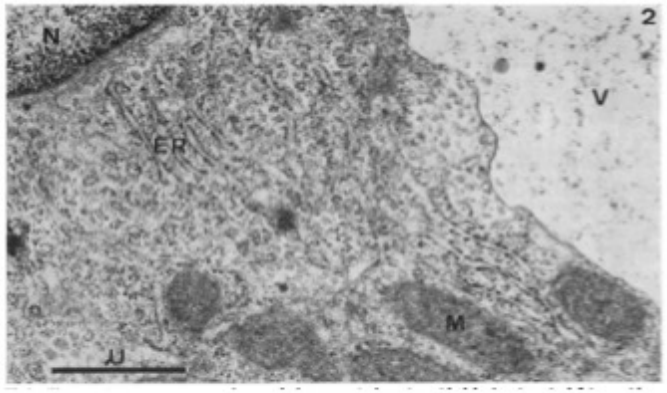
ARO-AAT designed to stop Z-AAT production by silencing AAT gene expression to:

- 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

Arrowhead RNAi Pipeline

Competitive Position	Drug	Disease	
First RNAi	ARO-AAT	Alpha-1 Liver Disease	
First RNAi	ARO-APOC3	Hypertriglyceridemia	
First RNAi	ARO-ANG3	Dyslipidemia	
First RNAi	ARO-ENaC	Cystic Fibrosis	
First RNAi	ARO-HIF2	Renal Cell Carcinoma	
Leading RNAi	ARO-HBV	Hepatitis B	Partnered with Janssen
First RNAi	AMG 890	Cardiovascular Disease	Partnered with Amgen
Undisclosed Target	ARO-AMG1	Cardiovascular Disease	Partnered with Amgen

AROAAT1001 Clinical Study in Healthy Volunteers

TWO PART STUDY

DOUBLE BLIND

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

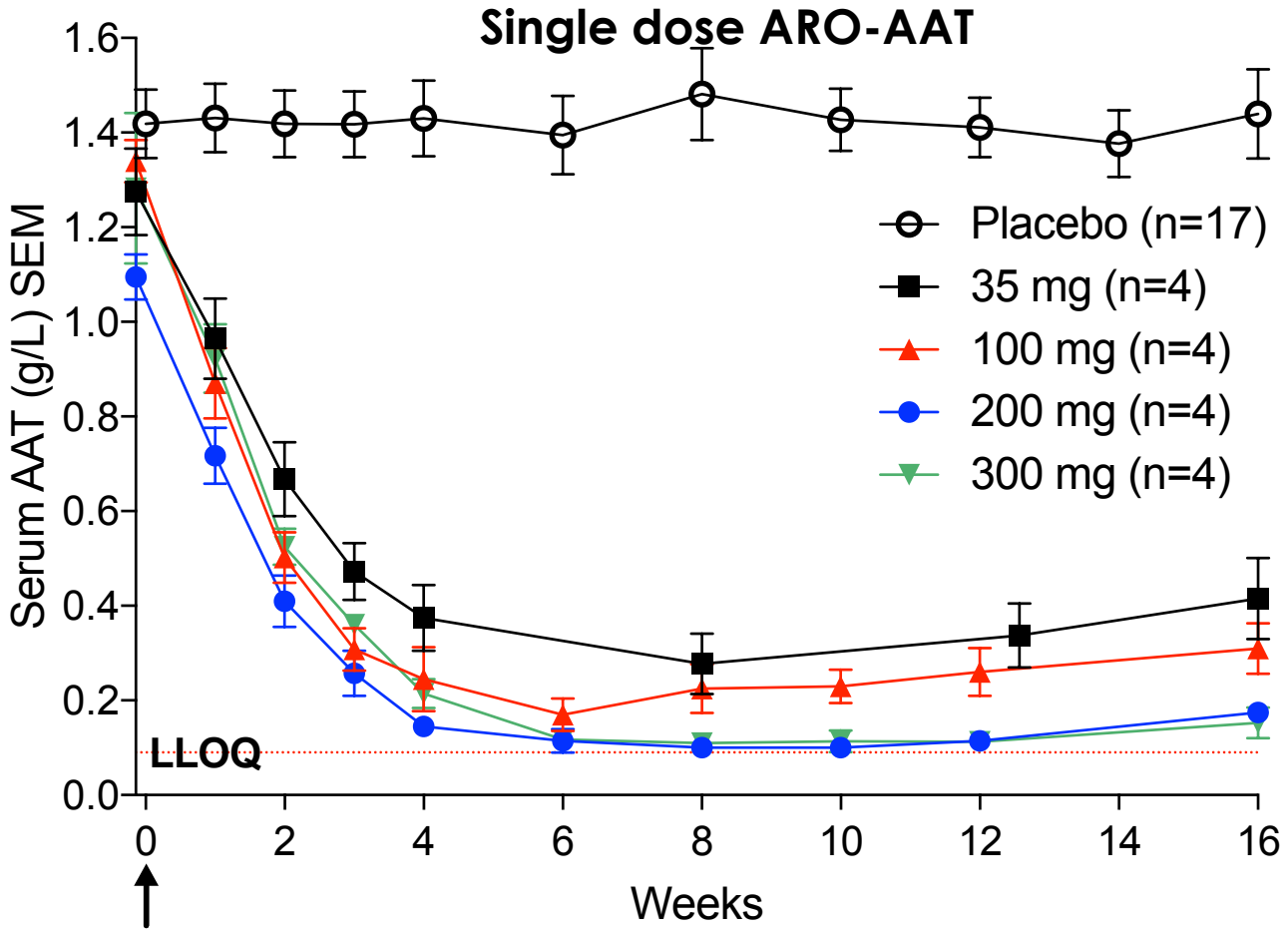
UNBLINDED

- No placebo
- 3 groups
  - ***Single doses*** of 100, 200 and 300 mg of ARO-AAT
- Assessments of safety, tolerability, depth and duration of AAT reductions after a single dose

ARO-AAT Phase 1, NHV Safety Summary

- 45 NHVs received at least 1 dose
- No serious or severe adverse events
- Mild injection site reactions in ~12% of injections (typically self limited, resolve in 48 hours)
- No dose related difference between active and placebo in lung function
- No adverse platelet/clotting related findings
- No adverse kidney findings

ARO-AAT Phase 1, NHV SAD/MAD study



Supports quarterly or less frequent dosing

U.S. IND filed for Phase 2/3 ARO-AAT study

AROAAT2001 Phase 2 Study Design

Phase: Adaptive Phase 2/3 Study

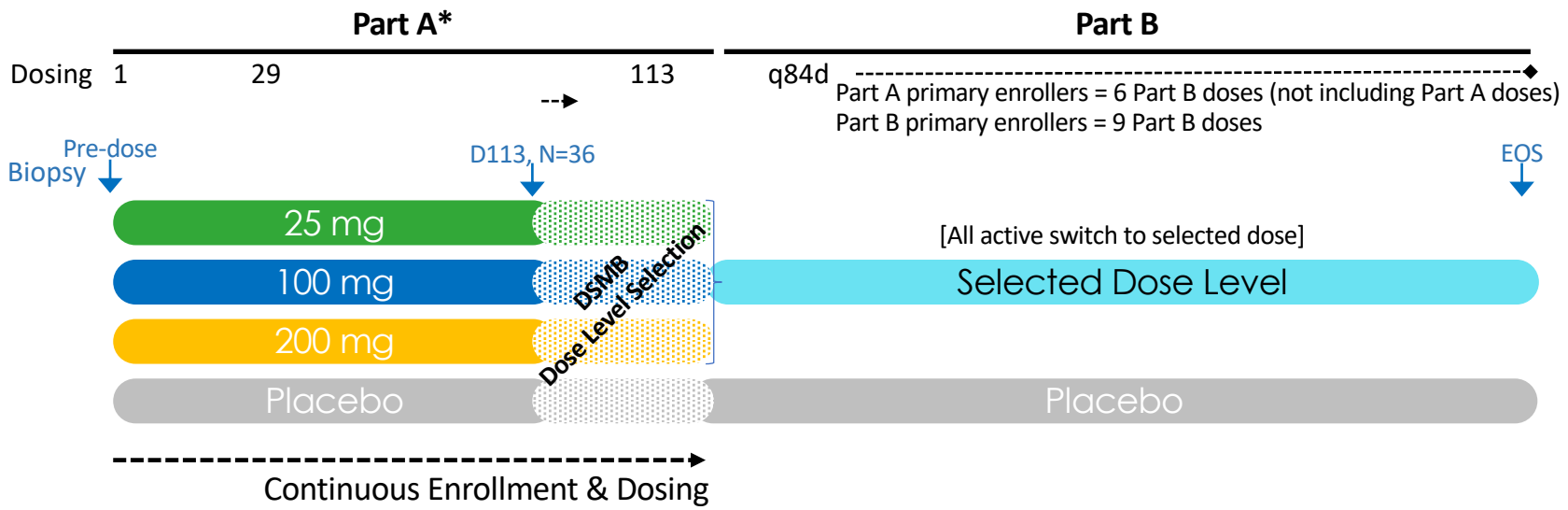
Location: Multiple sites in UK, EU **and US**

Study Design:

- Multi-center, multi-dose, placebo-controlled, adaptive
- Drug: ARO-AAT Injection (ARO-AAT) PLACEBO: 0.9% Normal Saline
- Route of administration: Subcutaneous Injection
  - Dosing on Days 1, 29 and 113 (and every 84 days thereafter in Part A, 6 doses every 84 days in Part B)

AROAAT2001 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 1st 36 will require D113 biopsy.

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

AROAAT2001 Study Objectives

Primary Objectives (Part A):

- To select a single dose level for use in Part B of the study based on a combined evaluation of safety and pharmacodynamic dose response in each Part A dose

Primary Objectives (Part B):

- To evaluate efficacy (as assessed by the proportion of ARO-AAT treated patients relative to placebo achieving a 2-point improvement in a histologic grading scale of alpha-1 antitrypsin deficiency associated liver disease AND no worsening of liver fibrosis based on end of study biopsy).

AROAAT2001 Key Inclusion/Exclusion Criteria

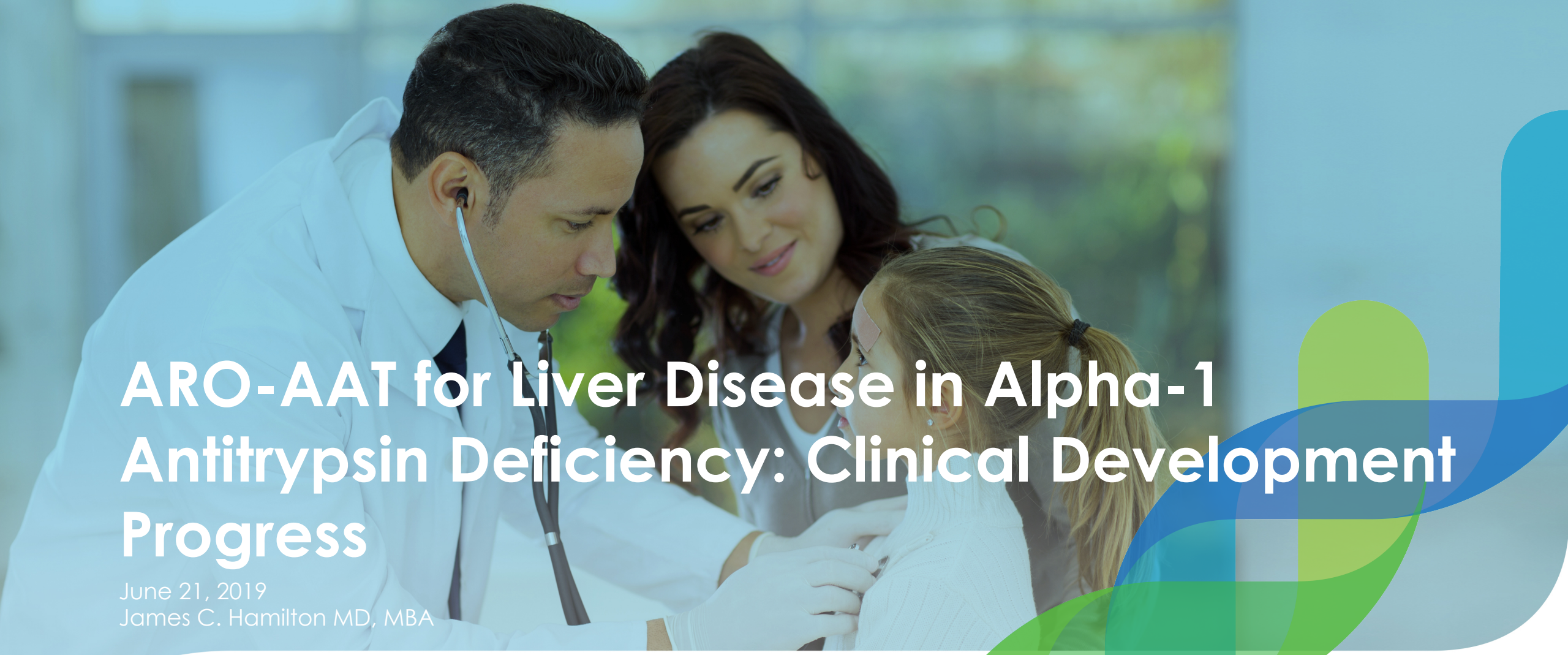
- Age 18-75 with PiZZ genotype AATD (study screening includes genotype)
- F2 or F3 (e.g. moderate to advanced) liver fibrosis
- Non-smoker
- No diagnosis of liver cirrhosis (at least not in this study)
- FEV1 < 65% predicted at Screening is exclusionary
- Augmentation use is allowed

AROAAT2001 Study Status

- Clearance from U.S. FDA and several European regulatory authorities to start study
- Sites opening in U.S./EU with plans to start screening patients next month

In Conclusion…….

- While not as well historically characterized as lung disease, AATD Liver disease can be silently devastating
- Thanks largely to alpha-1 researchers and the Alpha-1 Foundation the importance of alpha-1 liver disease has been revealed
- AROAAT2001 is the first trial designed to potentially serve as a pivotal study for US approval
- The trial is FDA approved and centers should be open and enrolling in coming weeks



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