Arrowhead Pharmaceuticals

World Orphan Drug Conference

April 25, 2018

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Safe Harbor Statement

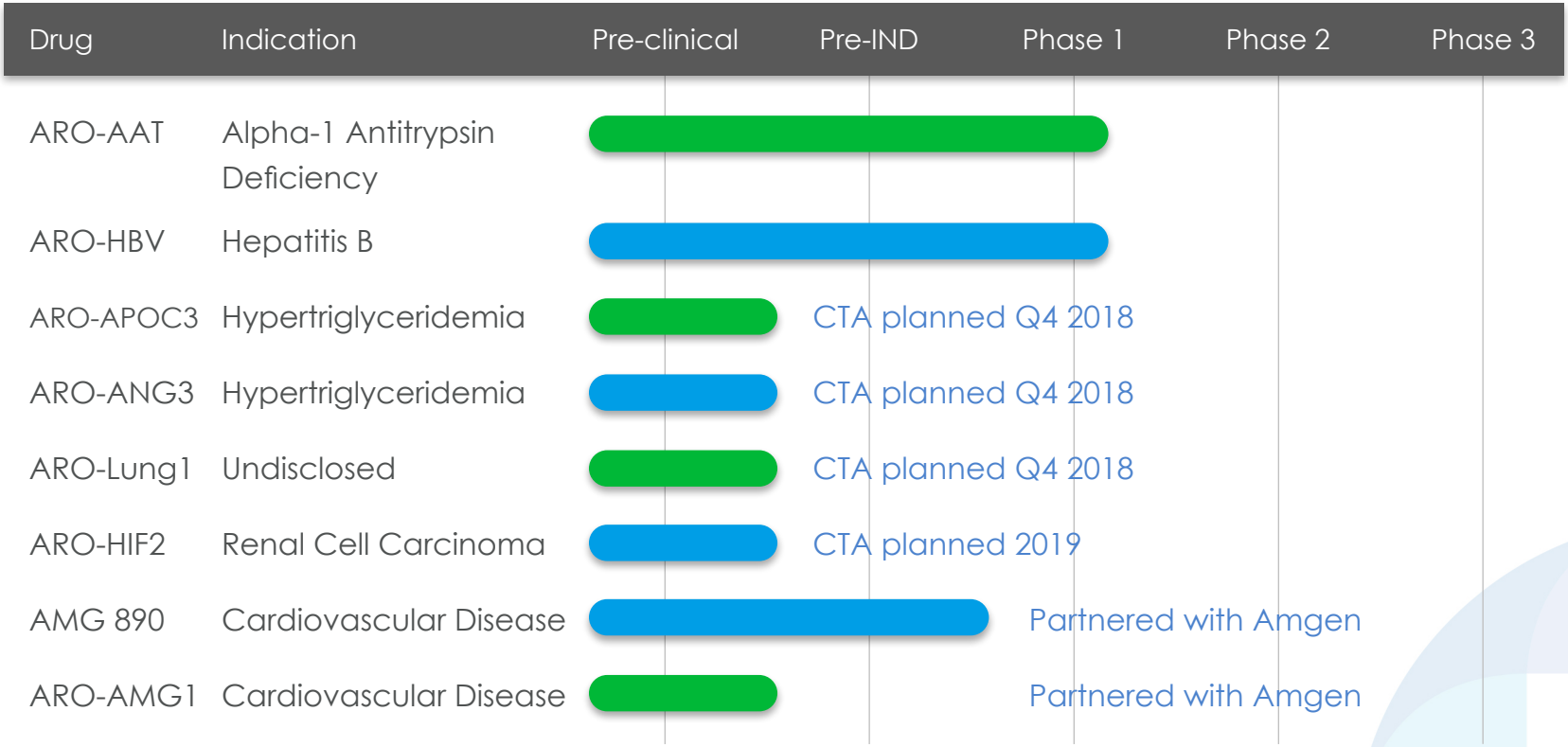
This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and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

Arrowhead Pharmaceuticals

Our mission is to treat intractable medical conditions by silencing the genes that cause them

ARWR - NASDAQ Global Select	
Recent Price (4/24/18)	$6.52
Market Capitalization	~$570m

Pipeline


Drug
Indication
Pre-clinical
Pre-IND
Phase 1
Phase 2
Phase 3
ARO-AAT
Alpha-1 Antitrypsin Deficiency
ARO-HBV
Hepatitis B
ARO-APOC3
Hypertriglyceridemia
CTA planned Q4 2018
ARO-ANG3
Hypertriglyceridemia
CTA planned Q4 2018
ARO-Lung1
Undisclosed
CTA planned Q4 2018
ARO-HIF2
Renal Cell Carcinoma
CTA planned 2019
AMG 890
Cardiovascular Disease
Partnered with Amgen
ARO-AMG1
Cardiovascular Disease
Partnered with Amgen

RNAi: RNA interference

- Naturally occurring mechanism to downregulate gene expression

- Can be leveraged therapeutically to "turn off" production of disease-causing proteins
  - Highly specific: can target ***single*** gene
  - Lower potential for off-target effects than small molecules
  - Highly efficient catalytic process
  - Capable of long duration of activity
  - Validated in humans, launch of first approved RNAi drug expected in 2019

Targeted RNAi Molecules:
The TRiM™ Platform

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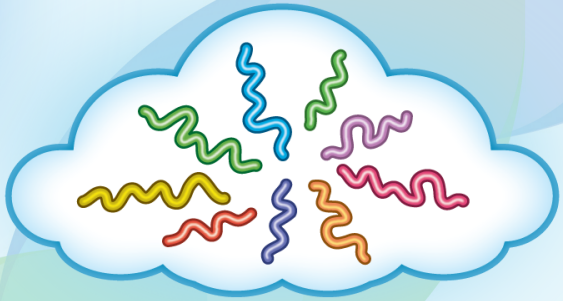
TRiM™ Chemical Modifications

Linker Chemistries

Targeting Ligands

Stabilization Chemistries



Structures to Enhance Pharmacokinetics

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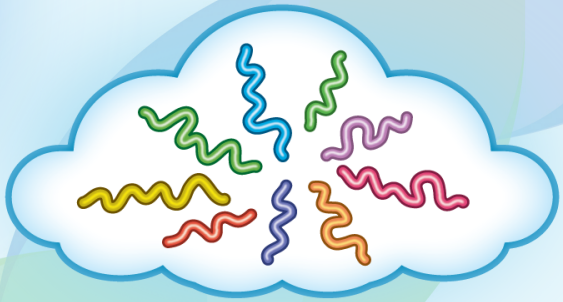
TRiM™ Chemical Modifications

Linker Chemistries

Targeting Ligands

Stabilization Chemistries



Structures to Enhance Pharmacokinetics

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First Liver-targeted Programs Using TRiM™

ARO-AAT

- For liver disease associated with alpha-1 antitrypsin deficiency
- Alpha-1 Foundation estimates >100k people with the ZZ AAT gene mutation in US
- Restart of clinical program that used prior DPC platform

In P1

ARO-HBV

- For treatment of chronic hepatitis B infection
- CDC estimates 350m chronic infections worldwide
- Restart of clinical program that used prior DPC platform

In P1/2

Given our knowledge of these diseases and clinical experience with 64 sites in 15 countries, we expect uncommon speed in the clinic

ARO-AAT

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Alpha-1-antitrypsin (AAT)

- An abundant serum protein primarily synthesized in the liver.
  - Thought that ~2 grams synthesized/day
- Physiologic function is inhibition of neutrophil proteases to protect host tissues during inflammation. This is especially important in the lung.
- Z mutant is the common disease variant
  - Point mutation that encodes a single aa substitution
  - Homozygous ZZ form: 1 in 2,000-3,500 births in US and Europe
  - Alpha-1 foundation estimates ~100,000 in the US, more in Europe

Alpha-1 Antitrypsin Deficiency

Mutation in AAT gene leads to mis-folding of the protein and poor export from hepatocytes: low levels in circulation and accumulation in liver

Pathophysiology

Lung

Tissues susceptible to damage by neutrophil proteases: COPD

↓

Treated with AAT enzyme replacement therapy today

Liver

Accumulation of mutant Z protein causes clinical liver disease

↓

No current treatment

Liver Pathophysiology

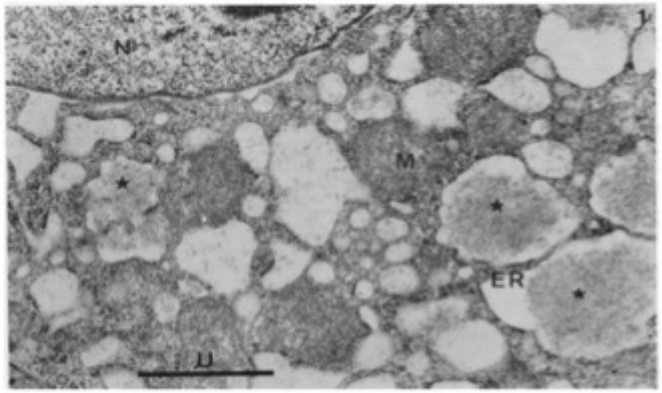
- Mutant Z protein accumulates in hepatocytes.
- Compensatory proteolytic pathways degrade most of the mutant Z protein.
- Some mutant Z molecules escape degradation
- Hepatocytes with the largest burdens of mutant Z protein suffer a cascade of intracellular damage ending in apoptosis.
- The chronic cycle of hepatocellular apoptosis and regeneration leads to fibrosis and organ injury.

ARO-AAT Mechanism of Action

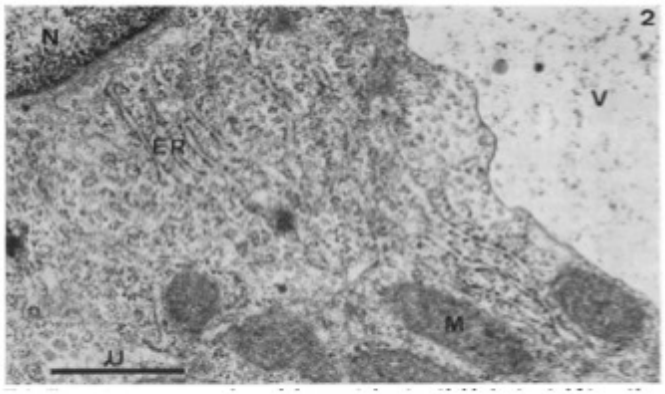
ARO-AAT designed to stop Z-AAT production by silencing AAT gene to:

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

PiZZ phenotype (diseased)



Pi null phenotype (normal)

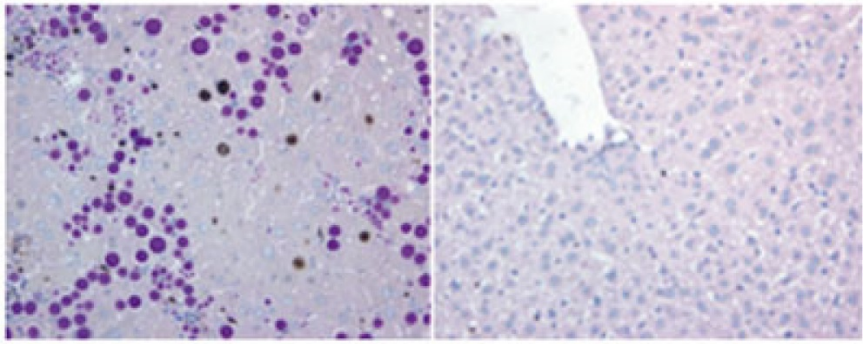


Feldmann G et al., *Gut* 1975

AAT transgenic mouse model

The transgenic PiZ mouse model expressing the human Z-mutant AAT gene (Z-hAAT) recapitulates the human phenotype

- Hepatocytes produce high levels of human Z-hAAT
- Z-hAAT forms polymers that accumulate in globules within the hepatocytes
- Presence of polymer stresses hepatocytes, eventually leading to HCC
- Liver phenotype worsens with age

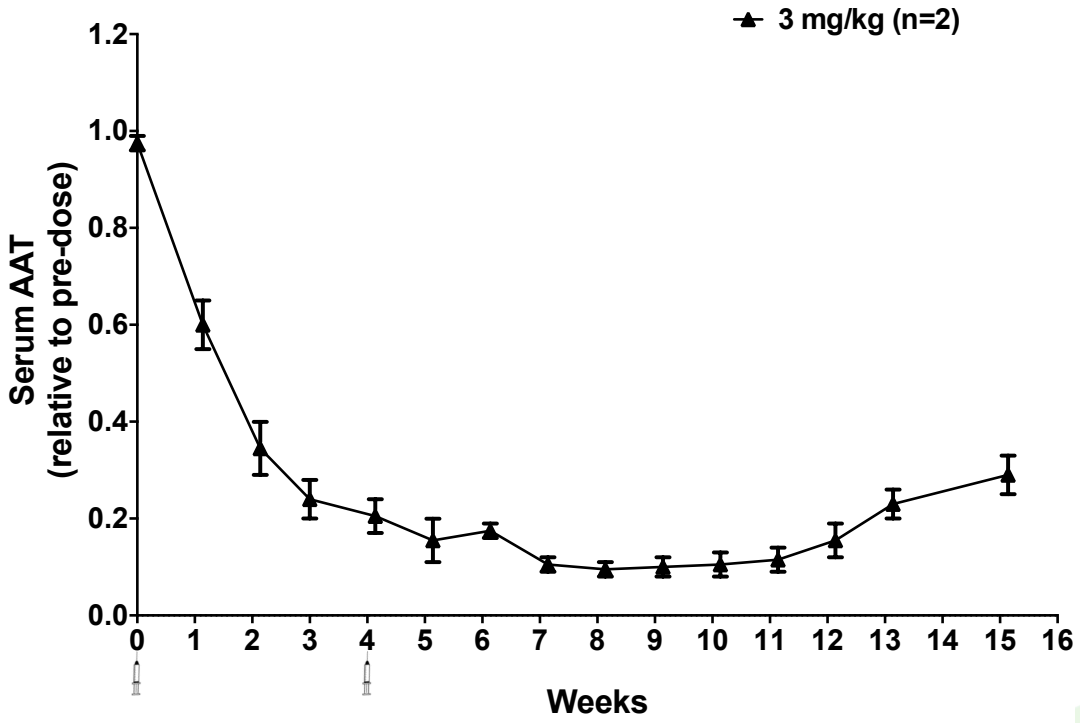


PiZZ **Wild Type**

Intervening at all stages of disease with RNAi showed benefit in mouse model

ARO-AAT: durable AAT knockdown in monkeys

- 92% maximum serum AAT knockdown achieved
- Knockdown sustained for 7+ weeks following second dose



Durable knockdown may support monthly or less frequent dosing

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ARO-AAT: Key Design Elements

The Wish List:

- ✓ Subcutaneous dosing, monthly or less frequent
- ✓ No need for endosomal escape agent
- ✓ Full suppression of liver AAT production
  - ✓ Deep and prolonged KD of plasma AAT levels
- ✓ Expectation of wide therapeutic index

Good activity and tolerability in humans (pending)

P1 data possible by EOY 2018

RNAi as an orphan drug modality

ARO-AAT: attractive candidate addressing a clear unmet need

- Biology is clear
  - Production of mutant protein causes liver damage in some patients; turning off that production could alleviate
- Monthly, or less frequent, SQ treatment expected
- Well tolerated in animals; good tolerability in humans expected

RNAi is an exciting modality for some orphan indications and we may be entering a period of rapid development/adoption

- Highly specific and efficient
- Lower potential for off-target effects than small molecules
- Capable of long duration of activity
- Validated in humans