Clinical Development of RNAi Therapeutics Targeting HBV and Alpha-1 Antitrypsin Deficiency

OTS, October 2018

arrowhead pharmaceuticals

Disclosures

- I am an employee and shareholder in Arrowhead Pharmaceuticals, Inc.

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.

Worldwide prevalence of chronic HBV infection

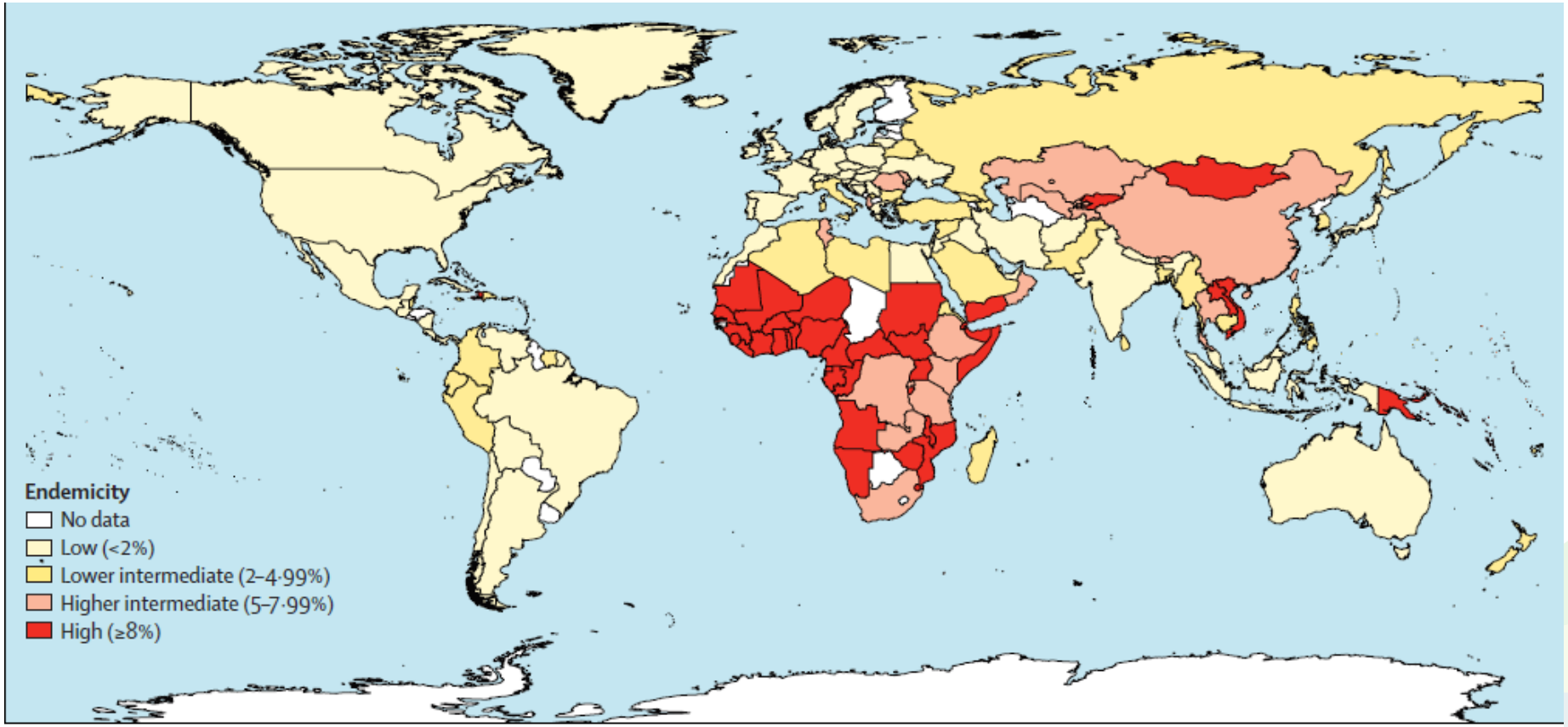


Figure 2: Global HBsAg endemicity (1957–2013)

Schweitzer et al. (2015), Lancet 386:1546-55

Globally an estimated 250-400 million people are chronically HBV infected

arrowhead pharmaceuticals

HBV – The Good and the Bad

- Vaccination has reduced the incidence of newly infected patients.
- NUC therapy reduces risk of cirrhosis and HCC but requires lifelong therapy.
- **Functional Cure (undetectable HBsAg and HBV DNA)** lowers risk of cirrhosis and HCC.
- **However** – functional cure is rare today (spontaneously ~0.5%/yr)
- ~1 million annual deaths due to HBV related decompensated cirrhosis or HCC.

arrowhead pharmaceuticals

HBV is Now Exploding with Innovation

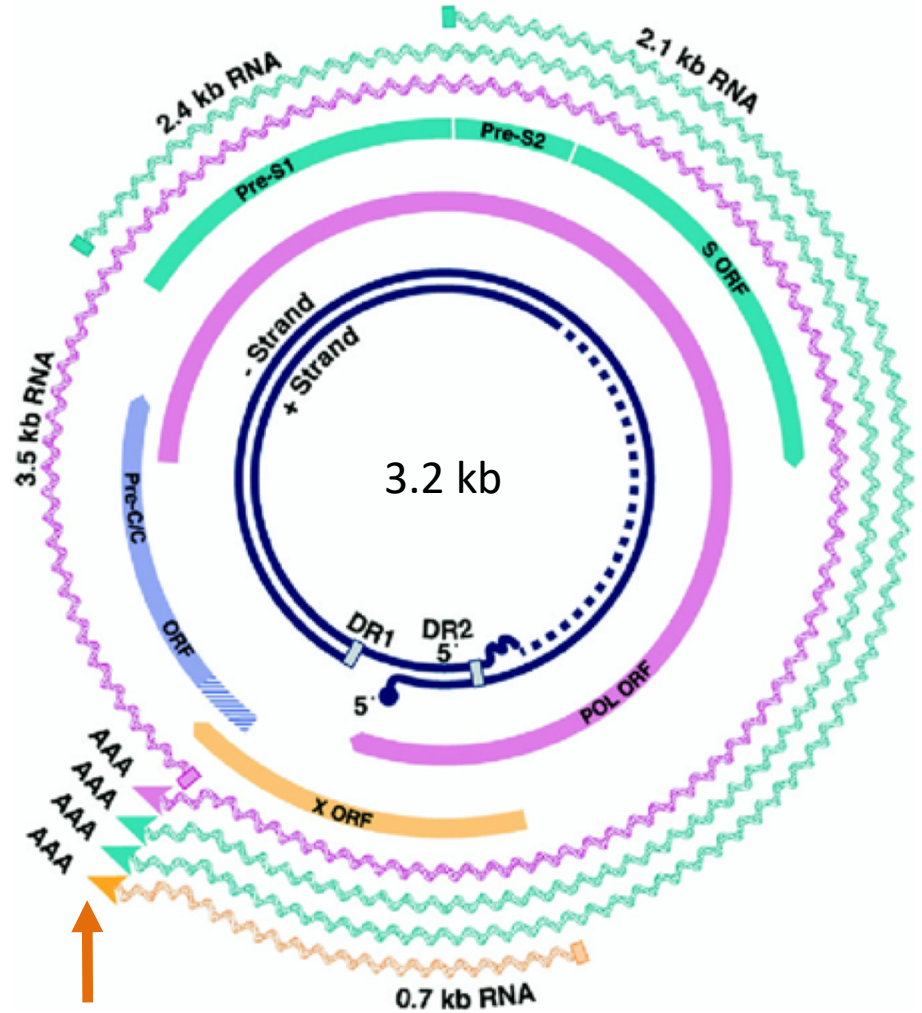
The Goal is Finite Therapy Leading to Functional Cure

- With the recent success in HCV, increased activity in HBV drug development **with an overall goal of functional cure with finite duration of therapy**

- US FDA, EMA, AASLD and EASL have agreed the general endpoint for approving new agents
  - SVR24 which will be DNA negativity ***and*** HBsAg negativity 24 weeks after cessation of all anti-virals agreed as the primary approval endpoint

arrowhead pharmaceuticals

Organization of the HBV genome makes it ideal for RNAi



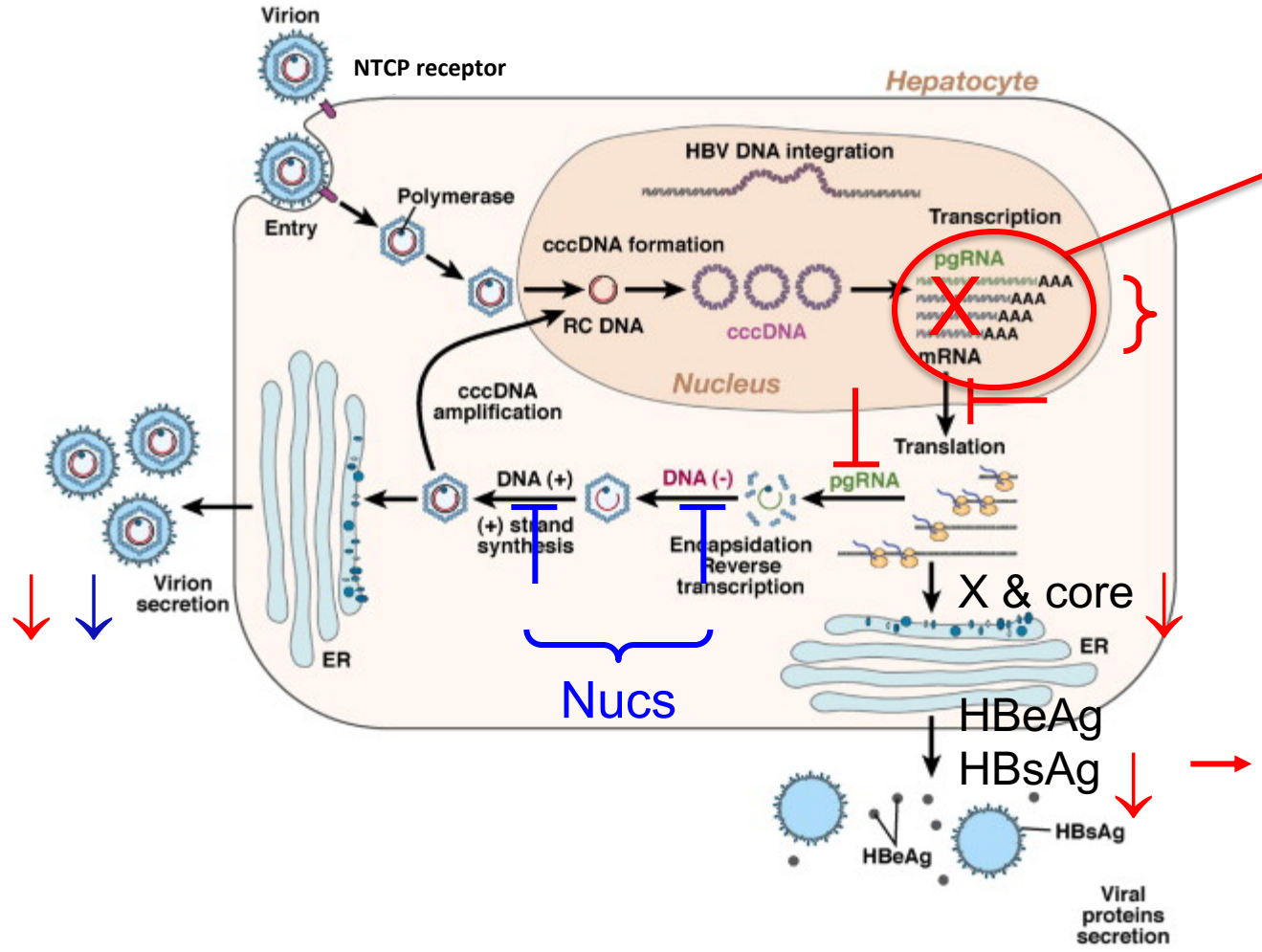
Same polyadenylation signal for all mRNAs

- **5 viral mRNAs**
  - 3.5 kb pre-genomic RNA
  - 3.5 kb pre-core mRNA
  - 2.4 kb pre-S1 mRNA
  - 2.1 kb pre-S2/S mRNA
  - 0.7 kb X mRNA
- **7 major proteins**
  - Polymerase (with reverse transcriptase function)
  - Core (HBcAg), forms capsid
  - e antigen (HBeAg), also called pre-core, a secreted protein
  - Large, medium and small surface proteins (HBsAg), form envelope
  - X protein (Transactivator)

arrowhead pharmaceuticals

Ghany & Liang (2007), *Gastroenterology* **132**: 1574-1585

RNAi Silence All HBV viral mRNA:



1. Large titers of HBsAg exhaust immune response
2. siRNA silences all viral mRNA transcripts.
3. Attack the viral life cycle on multiple levels and reduce HBsAg
4. **Hypothesis: revive host immune response**

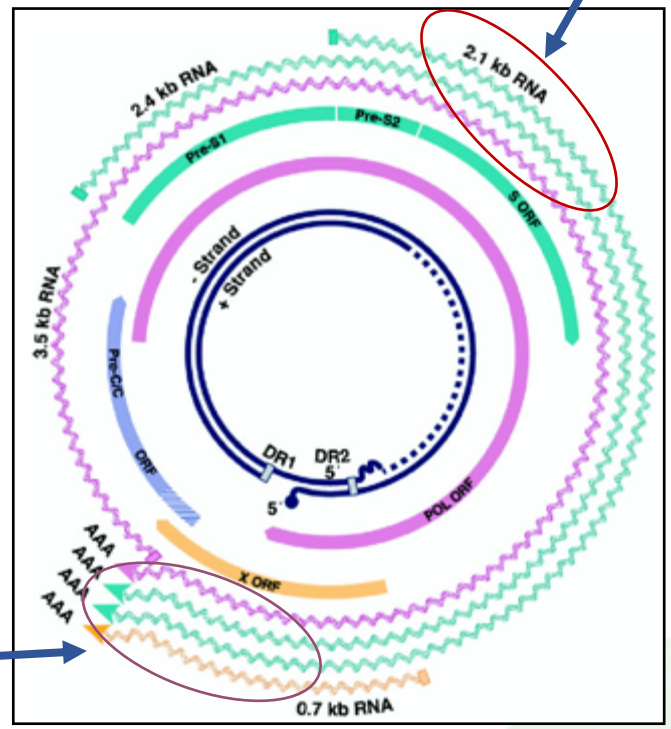
arrowhead pharmaceuticals

ARO-HBV

- Single siRNA can reduce all mRNA from cccDNA but can miss integrated HBV-derived mRNA
- S trigger designed to bind safely in integrated region should hit all mRNA except the 0.7 kb X mRNA
- Combination of X and S triggers → ARO-HBV
  - Greater genome coverage (99.6% full match in ~7000 HBV genomes)
  - Reduced chance of resistance
  - X antigen coverage

New S Trigger

HBV Transcript Map



Validated X Trigger

Ghany & Liang (2007), *Gastroenterology* **132**: 1574-1585

arrowhead pharmaceuticals

AROHBV1001 Clinical Study in Healthy Volunteers and HBV Patients

NHVs: DOUBLE BLIND

- SAD design
  - 35, 100, 200, 300, 400 mg
  - 4 active, 2 placebo
- Assessments of safety, tolerability, PK through Day 29

CHBs: OPEN LABEL

- MAD design
  - Three doses, Q28 days
- Four dose levels:100, 200, 300, 400 mg
  - Initial design of 4 per cohort
- Assessments of safety, tolerability, depth and duration of viral antigens, HBV DNA, RNA through Day 113.

CHB patient AE Table

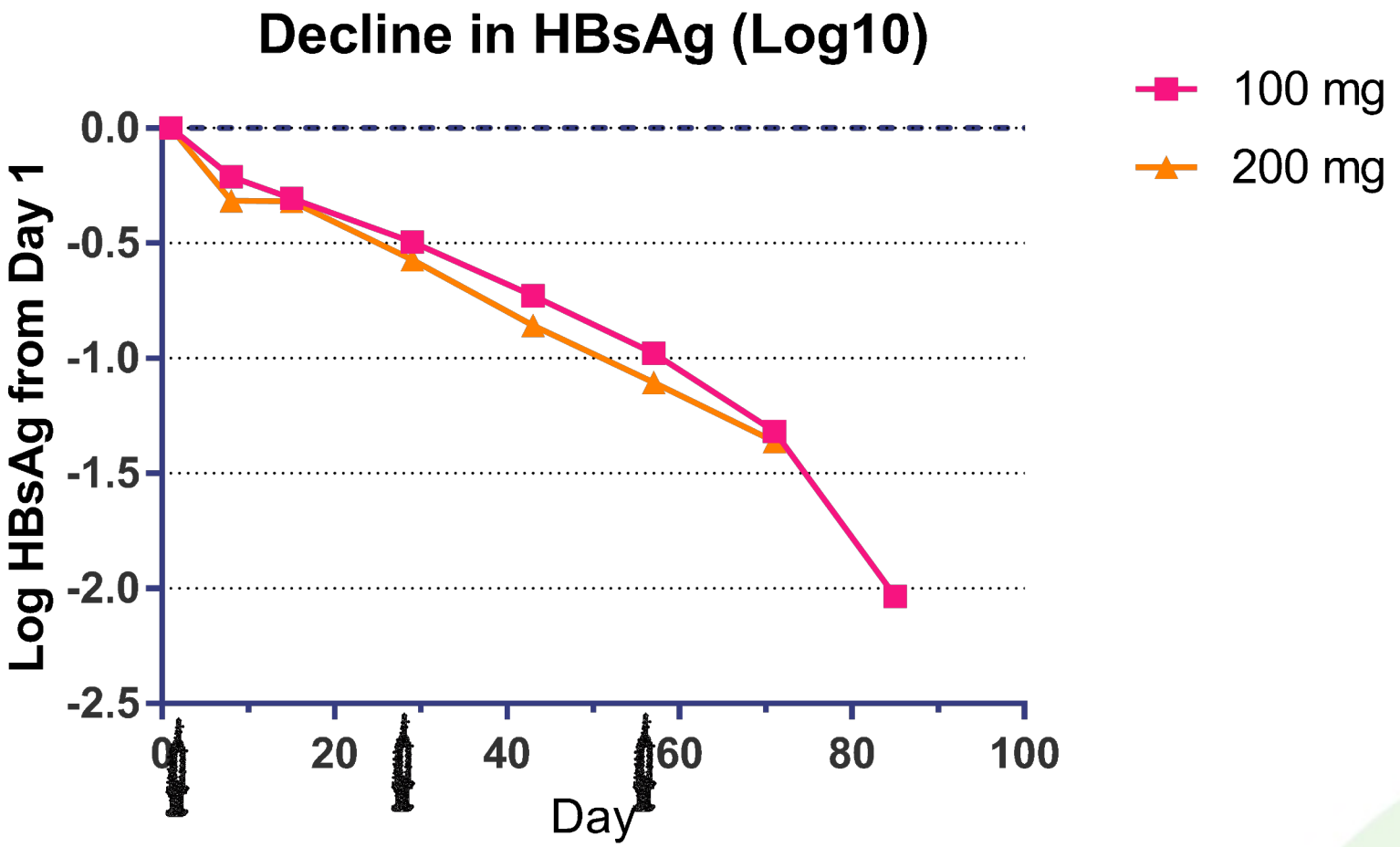
AEs in >1 subject (data cut 8/24/2018)

AROHBV1001 HBV Patients	**Cohort 2b, 100mg X3 Q28 days**	**Cohort 3b, 200mg X3 Q28 days**	**Cohort 4b, 300mg X3 Q28 days**	**Cohort 5b, 400mg X3 Q28 days**	**Cohort 6, 100mg X3, Q2 wk**	**Cohort 7, 100mg X3 weekly**	**Cohort 8, e+ 300mg X3 Q28 day**	**Cohort 9, e+ 300mg X3 Q28 day**	**Cohort 10, 200mg X3 weekly**	**Cohort 11, 300mg X3 weekly**	**Total AEs**
AE Reported Terms	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	
Insect bites ankles, Flea bites on neck	1		1								2
Upper respiratory tract infection, Sore throat, Laryngitis, Dry cough	1		1		3	1			1		7
Erythema around injection sites, Injection site redness, Haematoma at injection site, Injection Site Bruise			1	2		2	1			1	7
Facial acne, acne							2				2
Headache, headache – intermittent			1			2					3
Raised Creatine kinase			1				1				2
TOTALS	**2**	**0**	**5**	**2**	**3**	**5**	**4**	**0**	**1**	**1**	**23**

arrowhead pharmaceuticals

HBsAg Reduction with ARO-HBV After 3 monthly Doses

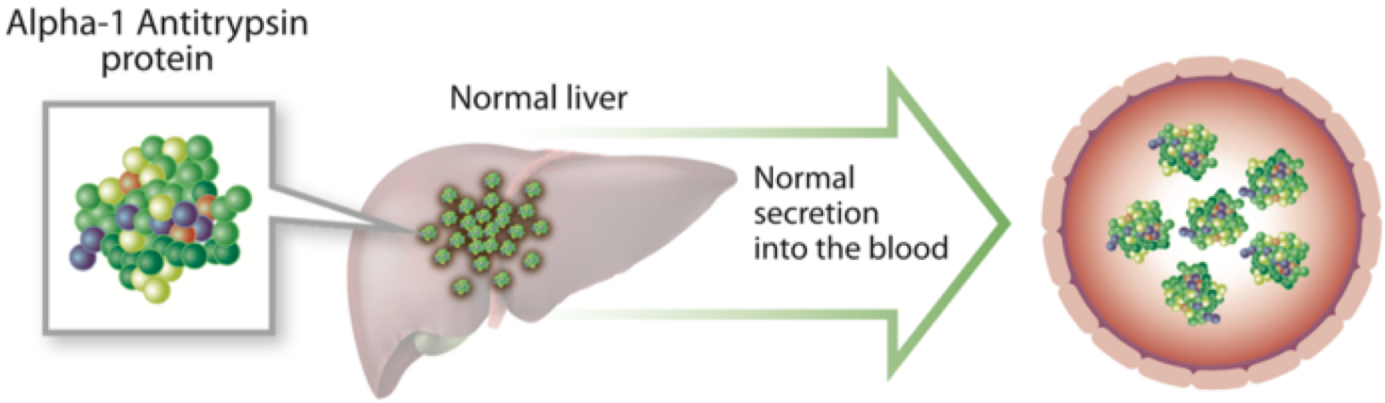
Includes cohorts with complete data through 14 days after 3rd dose



arrowhead pharmaceuticals

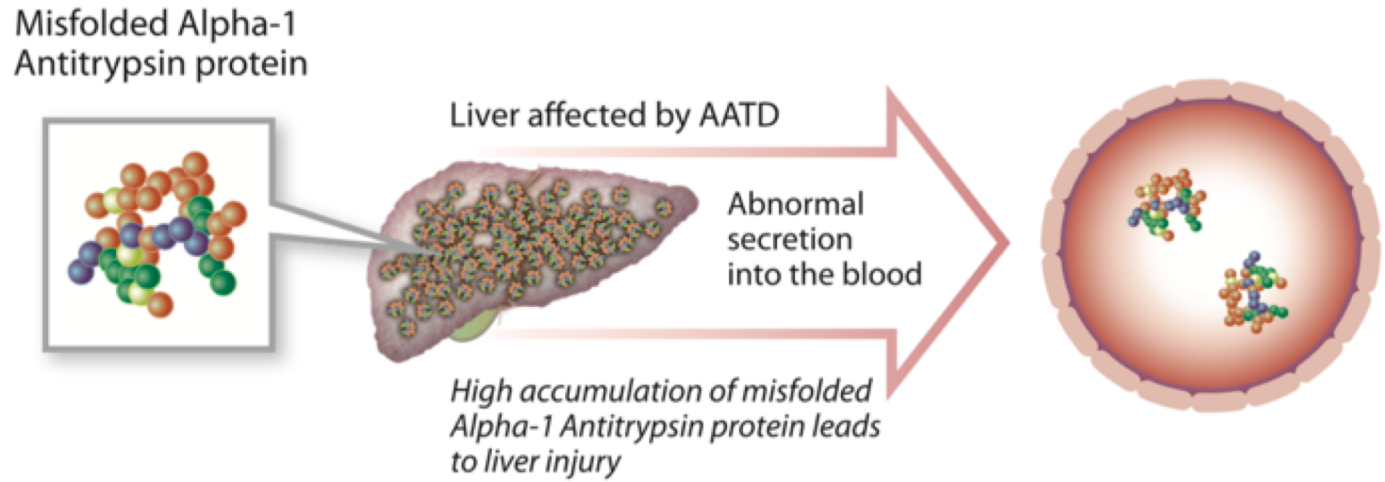
Alpha-1 Antitrypsin Deficiency

Normal AAT



Normal blood levels of normal protein protect lungs

Abnormal AAT (Z-AAT)



Low blood levels of abnormal protein leaves lung susceptible to damage from inflammation caused by inhaled irritants or infection

No current treatment

Treated with AAT protein replacement therapy today

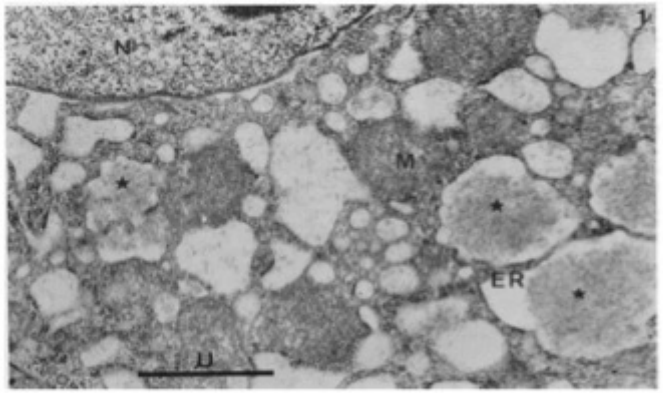
arrowhead pharmaceuticals

ARO-AAT, An Investigation Drug for AATD Liver Disease:
Mechanism of Action

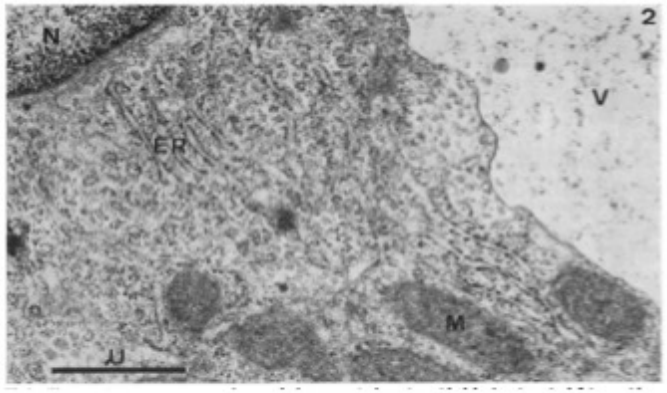
ARO-AAT designed to stop Z-AAT production by silencing AAT gene expression to:

- 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 pharmaceuticals

AROAAT1001 Clinical Study in Healthy Volunteers has 2 Parts

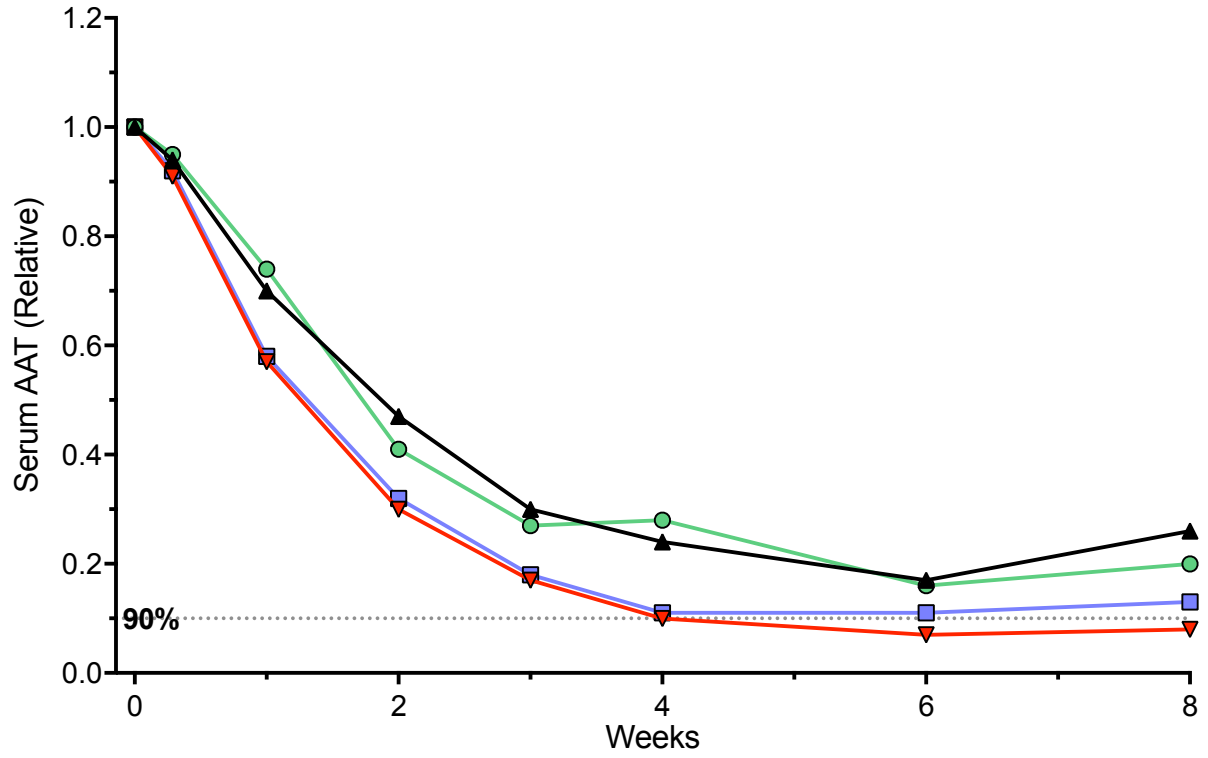
DOUBLE BLIND

- 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

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

Open Label AAT Plasma Data at 100 mg:
Single Dose, Healthy Volunteers



93%: Maximum Serum AAT Reduction achieved 6-weeks following a single dose
87%: Mean maximum serum AAT reduction achieved 6-weeks following a single dose

arrowhead pharmaceuticals

AROAAT1001 Safety Summary

- No SAEs, No Severe AEs
- Most AEs reported as mild (one moderate gastroenteritis)
- Mild injection site AEs occasionally reported
- No clinically meaningful adverse changes in BUN, creatinine, ALT, AST or total bilirubin
  - No pattern of adverse laboratory changes seen

Conclusions

- siRNA targeting HBV and AATD can be administered safely
- ARO-HBV demonstrates superior potency compared to 1st and 2nd gen compounds (ARC-520 and ARC-521)
- Proof of concept in form of RNAi induced viral antigen reduction and serum AAT reductions have been achieved using Arrowhead single molecule siRNA constructs.