Arrowhead Research

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Targeting Innovation

Jefferies Healthcare Conference
November 19, 2015

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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.

NASDAQ: ARWR

Recent price (November 17, 2015)	$5.49
Shares outstanding (including preferred as converted)	62m
Market cap	$ 340m
Cash (6/30/15)	$111 m

Clinical Programs in Hepatitis B and Liver Disease associated with Alpha-1 Antitrypsin Deficiency

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Comprehensive RNAi Platform Built Around Delivery

RNAi Chemistry

- Broad FTO for Canonical siRNA
- Broad FTO for Dicer siRNA
- Broad FTO for Meroduplex siRNA
- Broad FTO for UNAs
- Novel proprietary RNAi triggers
- Intracellular targeting ligands
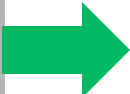 - ➢ Activity booster
- ALNY IP license for 30 targets

RNAi Delivery

- Highly Efficient / Potent
- Targetable
- Well tolerated

Technology from:
Roche, Novartis, Alnylam, Mirus Bio, City of Hope Cancer Center, Marina
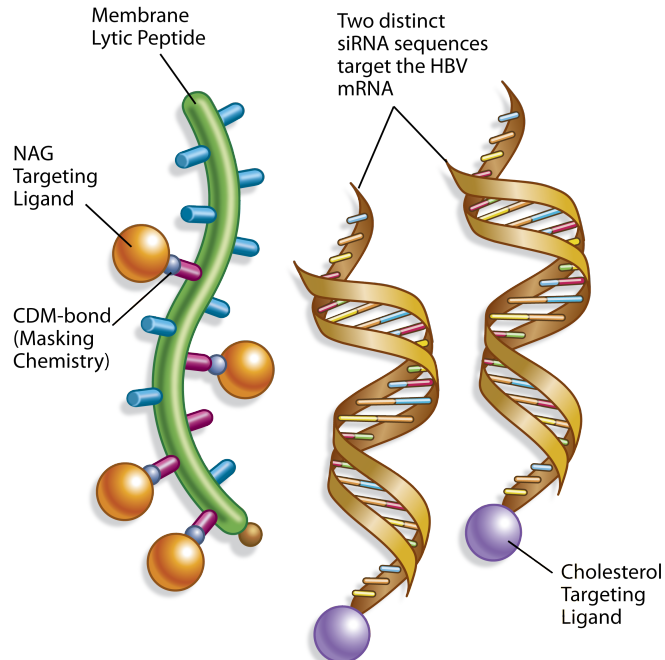
Clinical PoC with HBV and AAT Programs

Pipeline

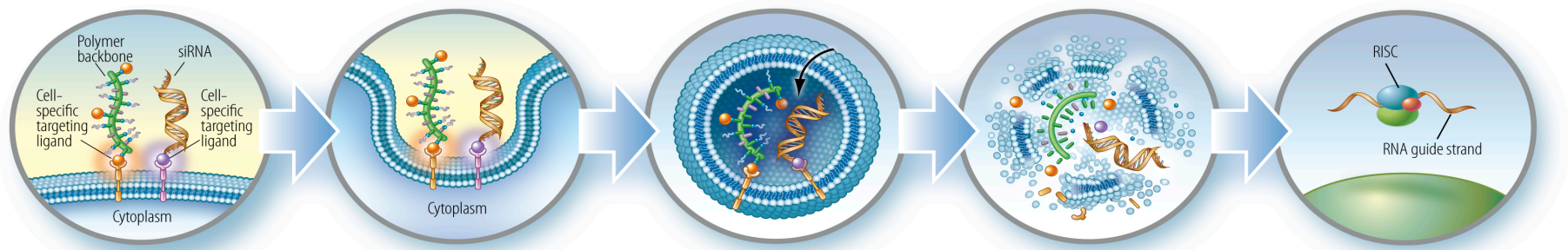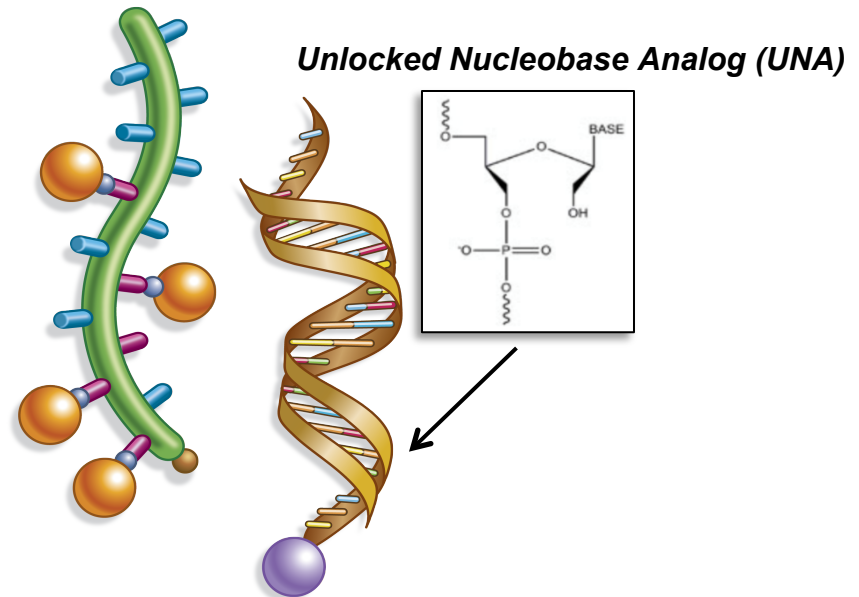| Program	Indication	Discovery	Pre-IND	P1	P2	P3
ARC-520	Chronic Hepatitis B					
ARC-521	Chronic Hepatitis B					
ARC-AAT	AATD Liver Disease					
ARC-F12	HAE and Thrombosis					
ARC-Hif2	ccRCC					
ARC-LPa	Cardiovascular Disease					

1. RNAi Platform play with attractive clinical candidates
2. Large HBV opportunity with novel first-to-the-clinic approach
   ➤ Clinical data has de-risked ARC-520 **and** platform
3. ARC-AAT: dosing P1 in Australia
4. Deep pipeline

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ARC-520 for chronic HBV infection

ARC-AAT for AATD associated liver disease

Membrane Lytic Peptide

Two distinct siRNA sequences target the HBV mRNA

NAG Targeting Ligand

CDM-bond (Masking Chemistry)

Cholesterol Targeting Ligand

Unlocked Nucleobase Analog (UNA)

BASE

Polymer backbone

siRNA

Cell-specific targeting ligand

Cell-specific targeting ligand

Cytoplasm

Cytoplasm

RISC

RNA guide strand

DPC polymer and siRNA attach to their respective targets on the cell surface.

DPC polymer and siRNA are taken up.

DPC polymer and siRNA are enclosed in an endosome. Low pH results in polymer unmasking.
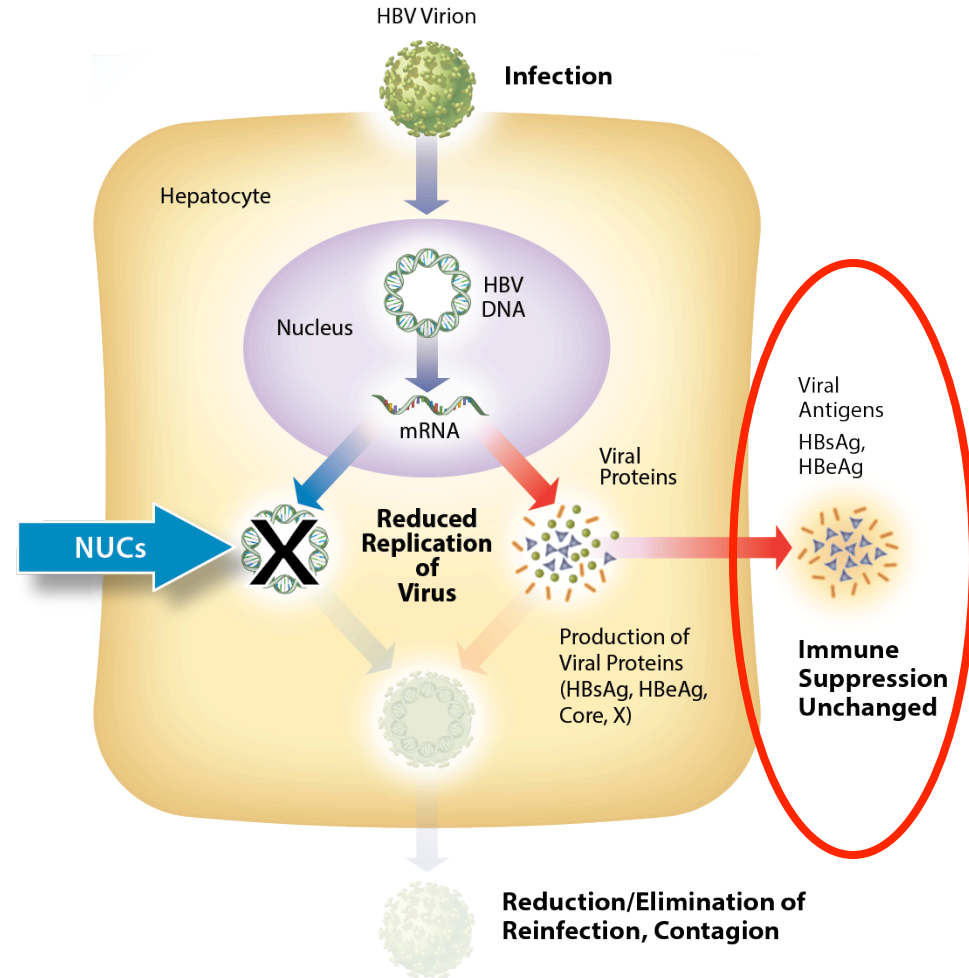
Polymer induces endosomolysis and release of siRNA payload into the cell cytoplasm.

siRNA engages the cell's interference machinery, resulting in knockdown of target gene expression.
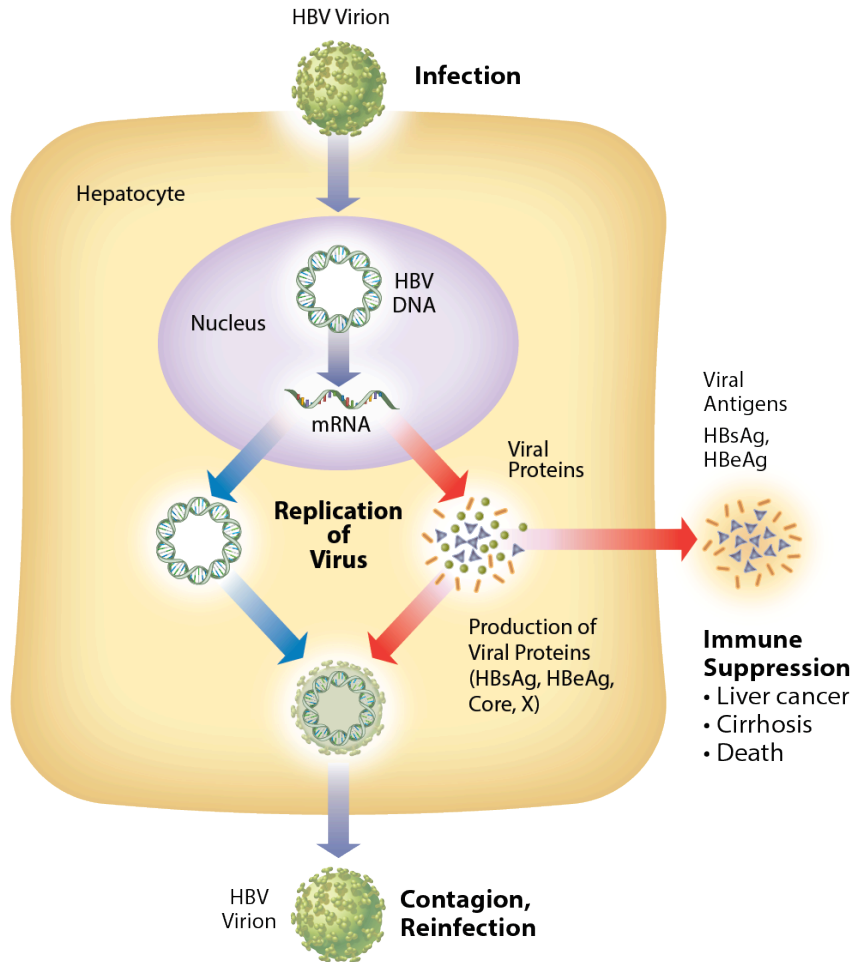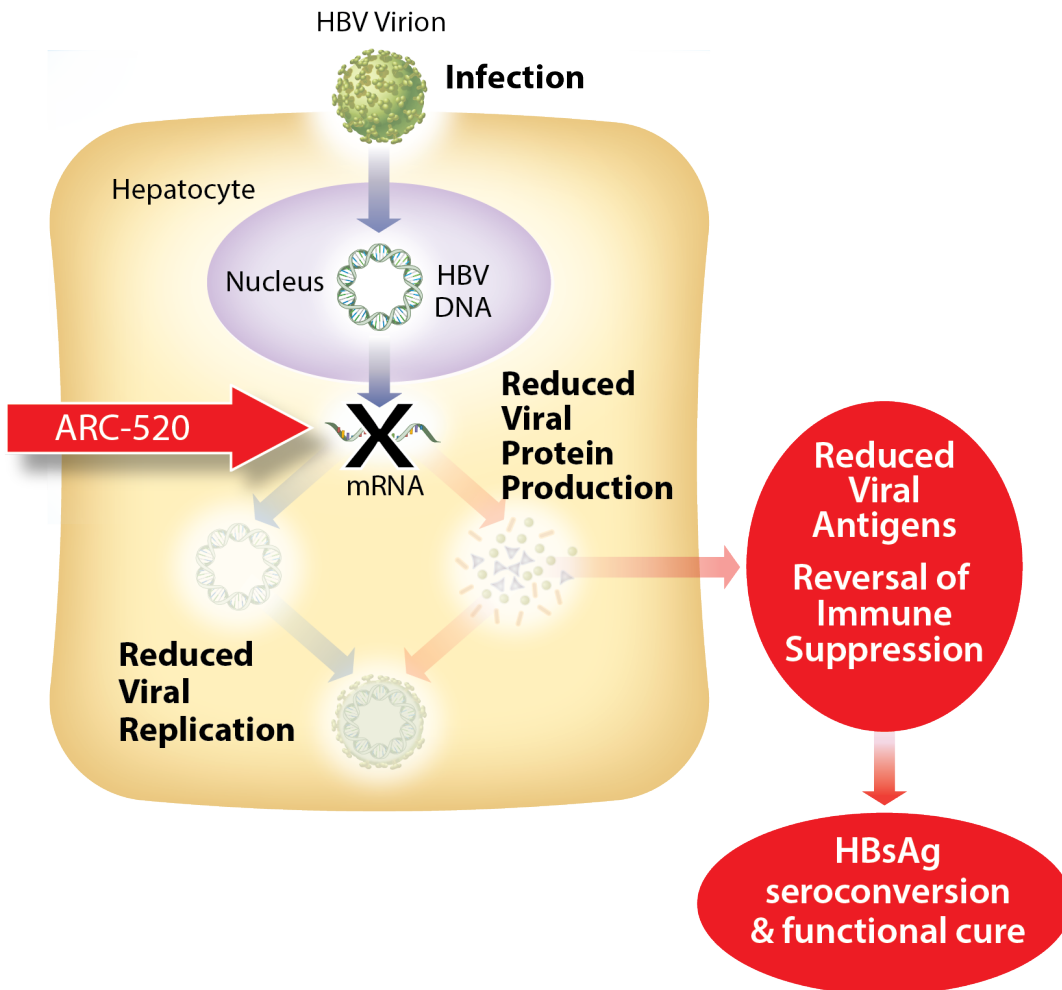
HBV Biology and Current Standards

NUCs require life-long therapy: not curative

Silence Entire HBV Genome

1. **"HBsAg Theory"**

   - Reducing HBsAg enables host immune system de-repression and long term control of virus

2. **Destabilizing Viral Function**

   - Silencing all antigens could destabilize normal viral function and enable host immune system de-repression and long term control of virus

Enable a Functional Cure

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Long term study in CHB chimps started to read out

Single dose ARC-520 studies in patients read out

Analyst Day September 24, 2015

ARC-520 de-risked
Platform de-risked
Changed the HBV textbooks
Expanded program: additional candidate

1. ARC-520 leads to deep HBsAg reduction

HBeAg status	HBsAg mean peak KD
HBeAg(+): 4 chimps	99% (2 log)
HBeAg(-): 4 chimps	81% (0.7 log)
HBeAg transitional: 1 chimp	87.4% (0.9 log)

2. Evidence of immune reactivation in 2 of the 4 HBeAg(+) chimps and 1 achieved sustained virologic effect off therapy

3. We concluded that different responses due to decrease of cccDNA during lifecycle of virus: HBsAg increasingly expressed by integrated DNA

Deep KD with ARC-520 and new paradigm for lifecycle of virus

- 84 humans have had single doses (or 2x2 mg/kg 2 weeks apart in six patients)
  - No AEs rated as serious or severe
  - No signs of end organ toxicity
  - No discontinuations due to AEs

- 9 chimps received 6 - 11 monthly doses ARC-520
  - No signs of any toxicity

ARC-520 has been very well tolerated

Think of the groups as quadrants
Defined by HBeAg status and NUC experience

	HBeAg+	HBeAg-
NUC Naïve	Naïve HBeAg+	Naïve HBeAg-
NUC Experienced	Experienced HBeAg+	Experienced HBeAg-

ARC-520 P2a

Cohort	Prior ETV	Pat Type	ARC-520 dose	Active / Placebo	Status
1	Yes	HBeAg neg	1.0 mg/kg	6/2	Complete
2	Yes	HBeAg neg	2.0 mg/kg	6/2	Complete
3	Yes	HBeAg neg	3.0 mg/kg	6/2	Complete
4	Yes	HBeAg neg	4.0 mg/kg	6/2	Complete
5	Yes	HBeAg pos	4.0 mg/kg	6/2	Complete
6	Yes	HBeAg pos	2 x 2.0 mg/kg	6/0	Complete
7	No	HBeAg pos HBeAg neg	4.0 mg/kg	6/0 6/0	Ongoing

Groups distinguished by lifecycle of the virus: cccDNA vs viral DNA integrated into host genome
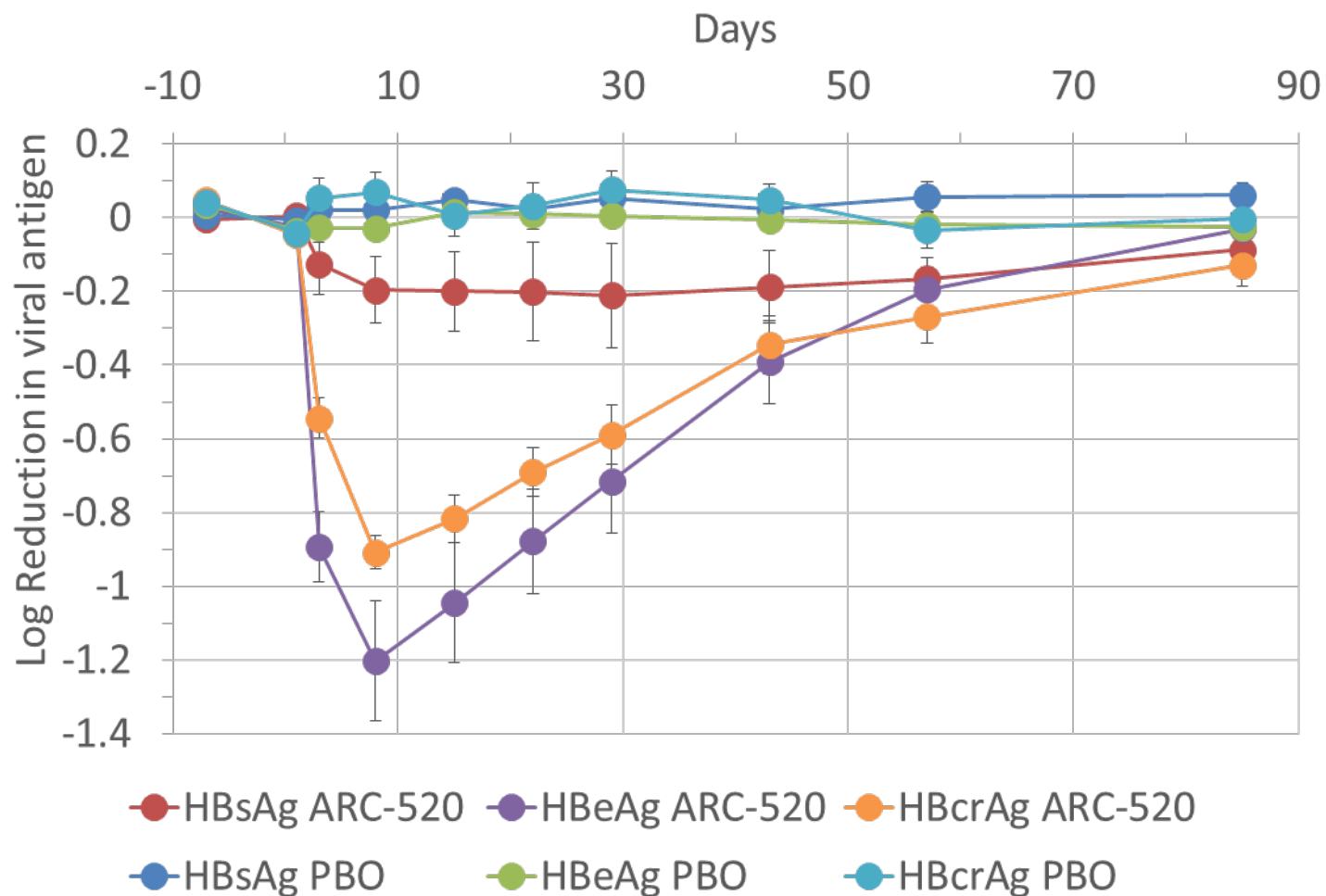
- Long-term NUC therapy decreases amount of viral cccDNA

- cccDNA decreases with transition from HBeAg+ to HBeAg-

NUC
Naïve

NUC
Experienced

**Deep KD of non-HBsAg
viral antigens in all 4 groups**

HBeAg+   HBeAg-

ARC-520 targets cccDNA; all non-HBsAg antigens are *only* expressed by cccDNA

Platform and drug validation

KD profiles in the 4 HBV groups

	HBeAg+	HBeAg-
NUC Naïve	Deepest HBsAg KD	Moderate HBsAg KD
NUC Experienced	Moderate HBsAg KD	Moderate HBsAg KD

HBsAg is expressed by *both* cccDNA *and* integrated DNA: NUC-naïve HBeAg+ patients are richest in cccDNA so demonstrate deepest HBsAg KD
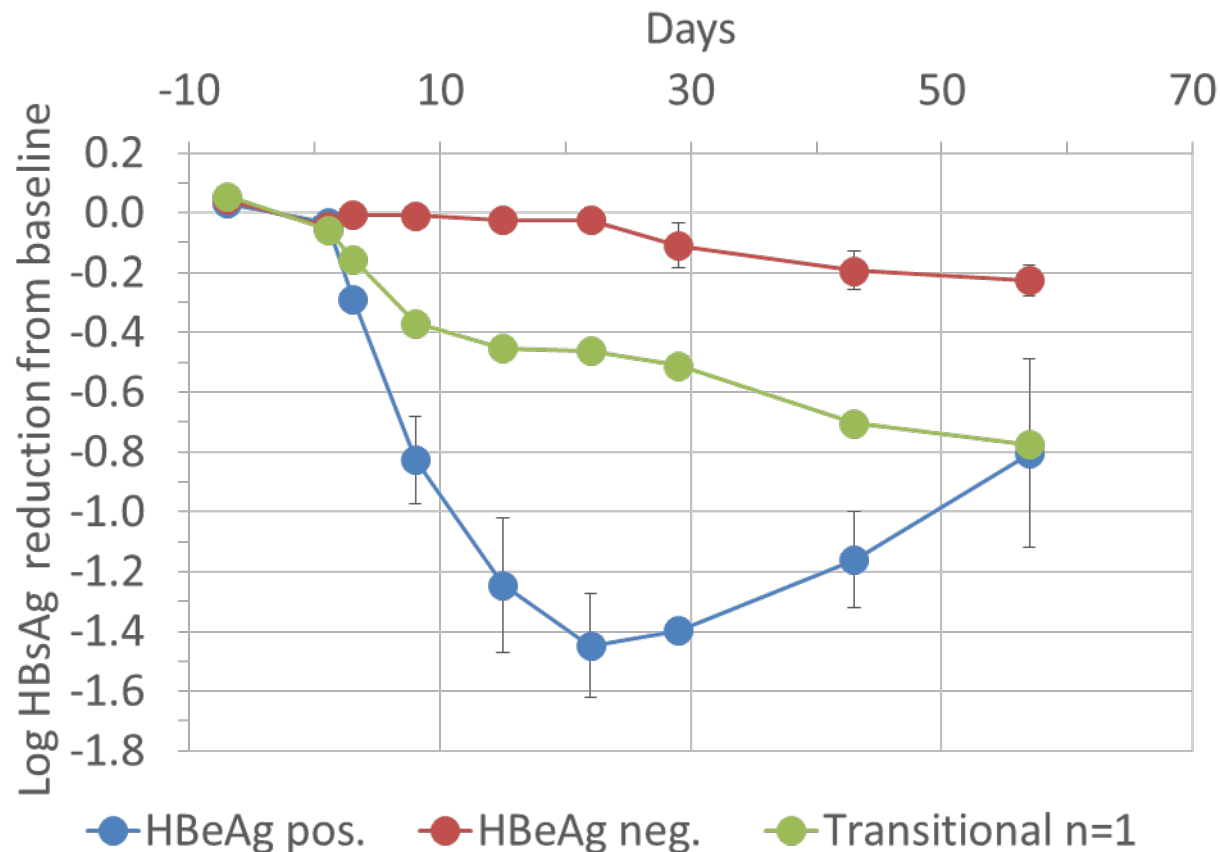
Transitional patient was HBeAg-pos. at baseline and HBeAg negative at days 3 to 43

More validation: deepest single dose KD ever demonstrated in humans with RNAi

- Well tolerated

- Deep HBsAg KD in treatment-naïve HBeAg+ patients
    - Max 99% HBsAg KD (1.9 log); mean nadir 97% (1.5 logs)
    - Speaks to "HBsAg theory" of achieving functional cure

- Clearly disrupts virus in NUC-experienced and HBeAg- patients
    - >1 log KD of HBeAg, HBcrAg, and presumably others
    - ARC-520 intended for multi-dose therapy: sustained measurable HBsAg KD and very deep KD of **all** other antigens could be important to reaching functional cure
    - Could be important beyond "HBsAg theory"

ARC-520 is very potent at silencing cccDNA: could be key component in achieving functional cure

NUC-naïve HBeAg(+) patients

will experience greatest HBsAg KD:

Large segment of the chronic HBV population

In U.S.
95% of estimated CHB are naïve

~50% estimated to be HBeAg(+)

In W. Europe
90% of estimated CHB are naïve

~33% estimated to be HBeAg(+)

Proprietary data from Clarion Healthcare, LLC

We have developed an additional candidate to:

(1) Ensure broader coverage of entire market;
(2) Provide 2 shots on goal

ARC-520	ARC-521

• Optimized for cccDNA KD
    • Clarity on KD and safety
• >1log KD in all antigens studied
• Began multi-dose studies
• Combo studies starting in Q4
with first IRB/regulatory approvals in hand
	• Safety expected = ARC-520
	• Optimized to include integrant KD
	• Validated in chimps
	    • Multi-log KD
	• Complement to ARC-520
	• IND or equivalent by June 2016

De-risked program with safety/activity of ARC-520, increased exposure to additional patient populations

HBV Program Next Steps

- **ARC-520 multiple dose P2b studies underway**

  ➢ Some open label, so flexibility in data release

- **ARC-520 Monarch combination studies start by EOY 2015**

  ➢ Initial regulatory approval in hand

  ➢ Open label, so flexibility in data release

- **ARC-521 in clinic in 2016**

  ➢ GLP tox underway

  ➢ Expect IND or equivalent by June 2016

Potentially important data coming out of multiple dose and combination studies

- AATD is a large scale orphan disease

  - Alpha-1 foundation estimates 100,000 in the US

- 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

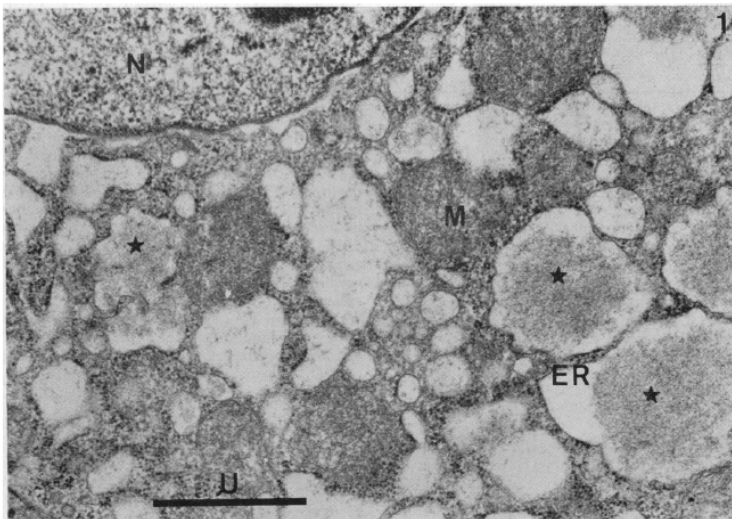| Lung	Liver
Tissues susceptible to damage by neutrophil proteases: COPD	Accumulation of mutant Z protein causes clinical liver disease
Controlled with enzyme replacement therapy	No current treatment

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

- Prevent accumulation of disease causing protein

- *Allow* clearance of accumulated protein

- *Prevent* repeated cycles of cellular damage and tissue repair.

- *Reverse* fibrosis associated with prior damage by allowing repair
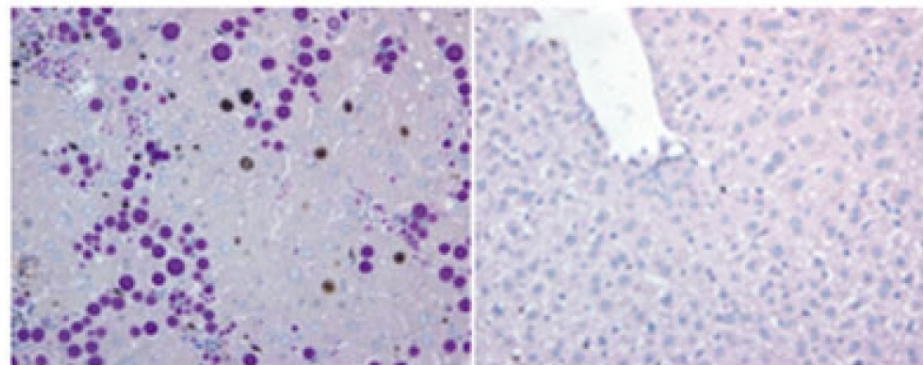
PiZZ phenotype (diseased)　　　　　　　　　　　　　　　**Pi null phenotype (normal)**

Feldmann G etal., *Gut 1975*
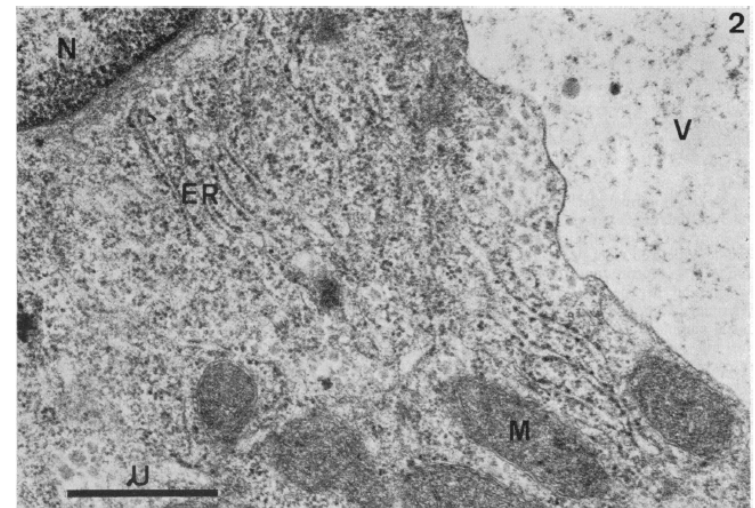
The transgenic PiZ mouse model expresses the human Z-mutant AAT gene (Z-AAT) and recapitulates the human AATD-associated liver phenotype:
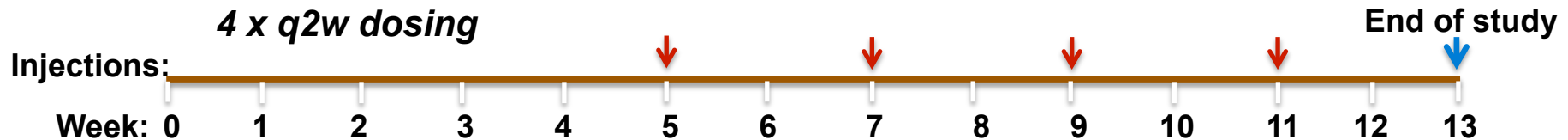
- Hepatocytes produce high levels of human Z-AAT

- Hepatocytes are unable to efficiently process and secrete the Z-AAT

- Z-AAT forms polymers that accumulate in large "globules" within the hepatocytes.

- These globules stress the hepatocytes, eventually leading to fibrosis and hepato-cellular carcinoma.
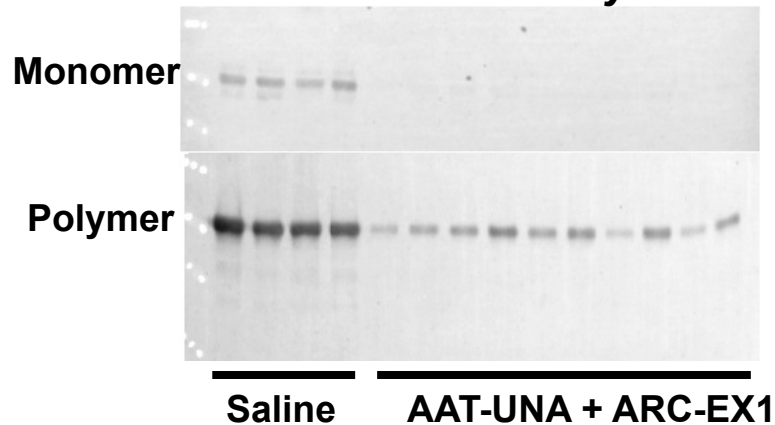

Male Piz   Male WT
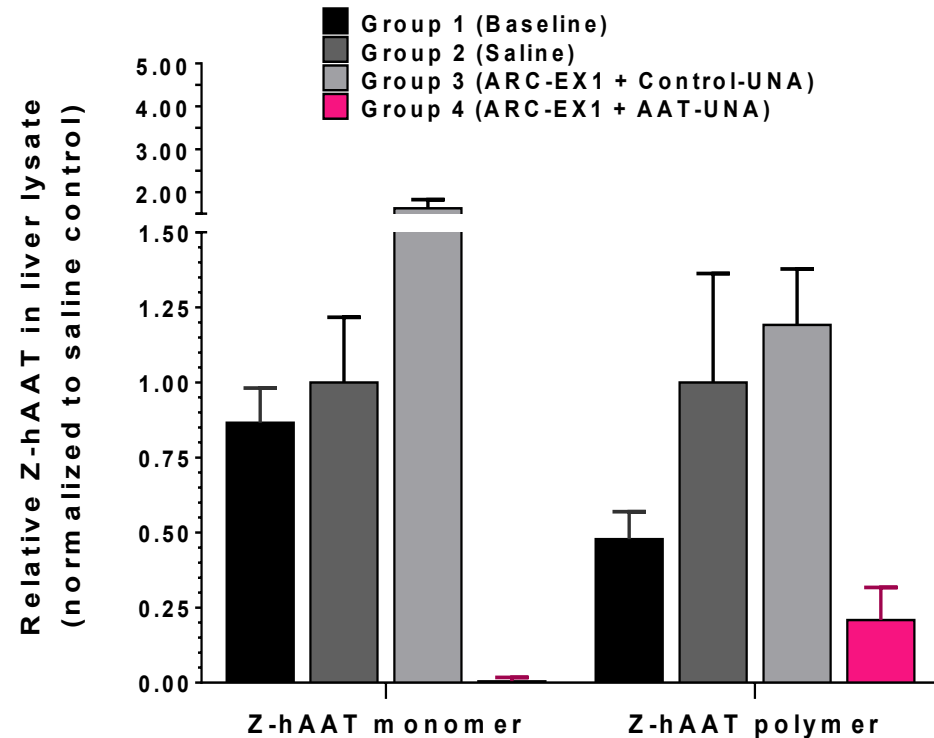
Rudnick DA et al., *Hepatology. 2004*

Reduction of Z-hAAT aggregates

4 x q2w dosing — End of study

Injections timeline — Week: 0 1 2 3 4 5 6 7 8 9 10 11 12 13

Western blot – liver lysate

Monomer

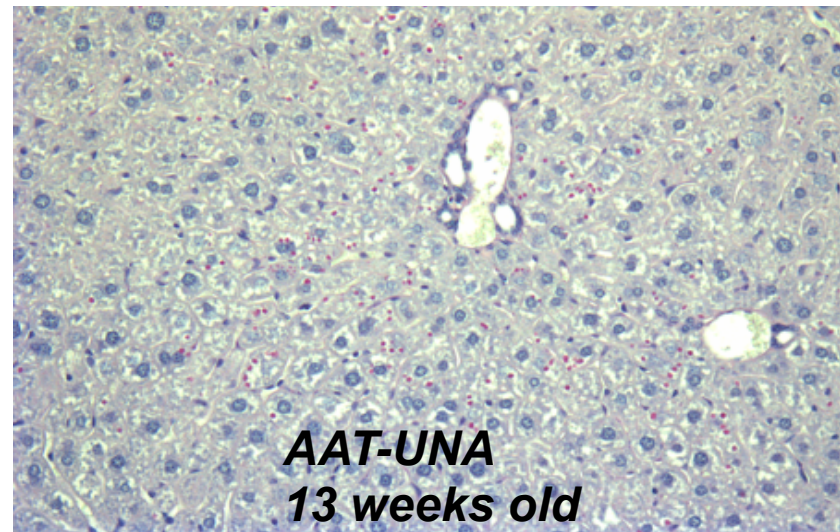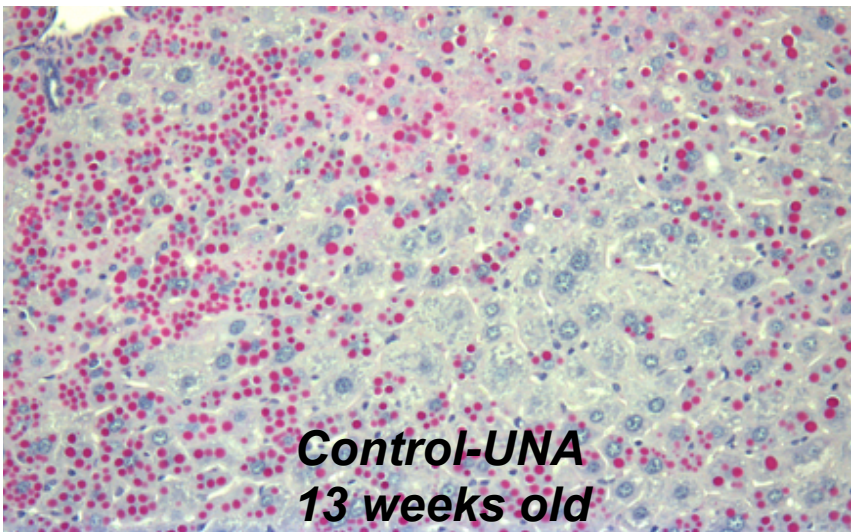Polymer

Saline | AAT-UNA + ARC-EX1

99% less soluble (monomer) Z-hAAT
79% less insoluble (polymer) Z-hAAT

Relative Z-hAAT in liver lysate (normalized to saline control)

- Group 1 (Baseline)
- Group 2 (Saline)
- Group 3 (ARC-EX1 + Control-UNA)
- Group 4 (ARC-EX1 + AAT-UNA)

Z-hAAT monomer — Z-hAAT polymer

Male and female PiZ mice

25

Reduction in Z-AAT Liver Globules

4 x q2w dosing

*Baseline
5 weeks old*

*Saline
13 weeks old*

*Control-UNA
13 weeks old*

*AAT-UNA
13 weeks old*
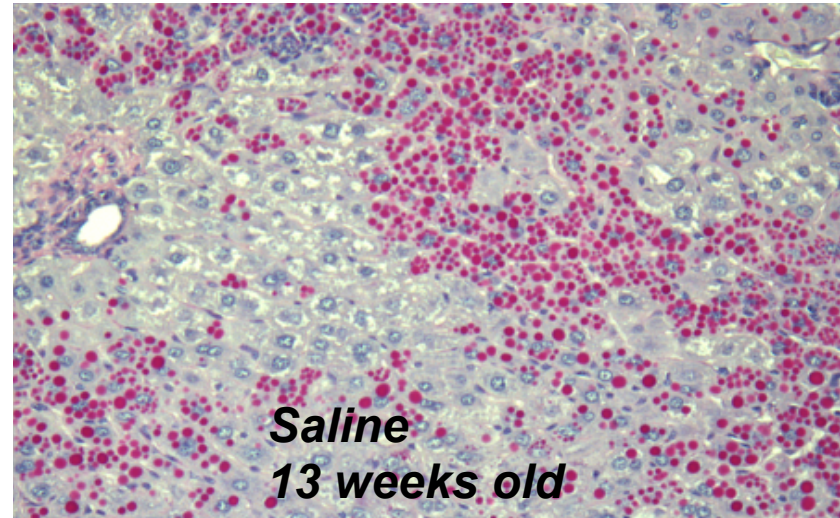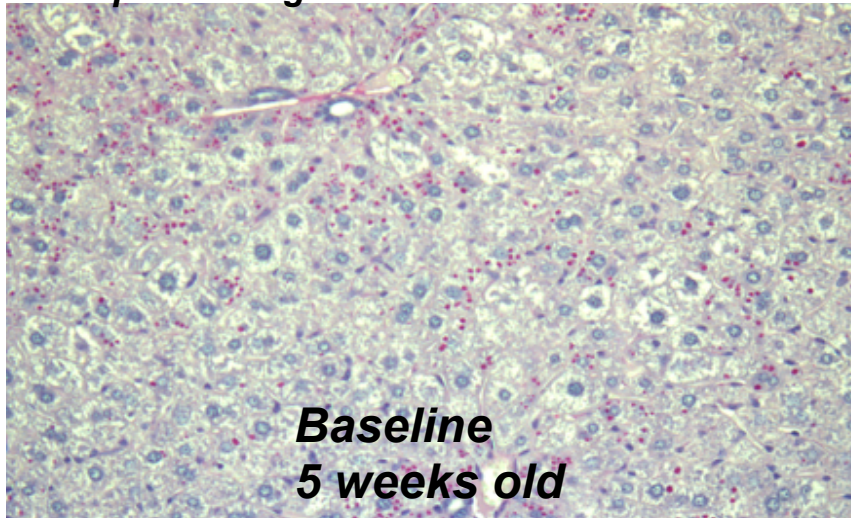
Liver globule burden is reduced after just two months of ARC-AAT treatment

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6 mg/kg AAT-UNA
3 mg/kg ARC-EX1
N=2
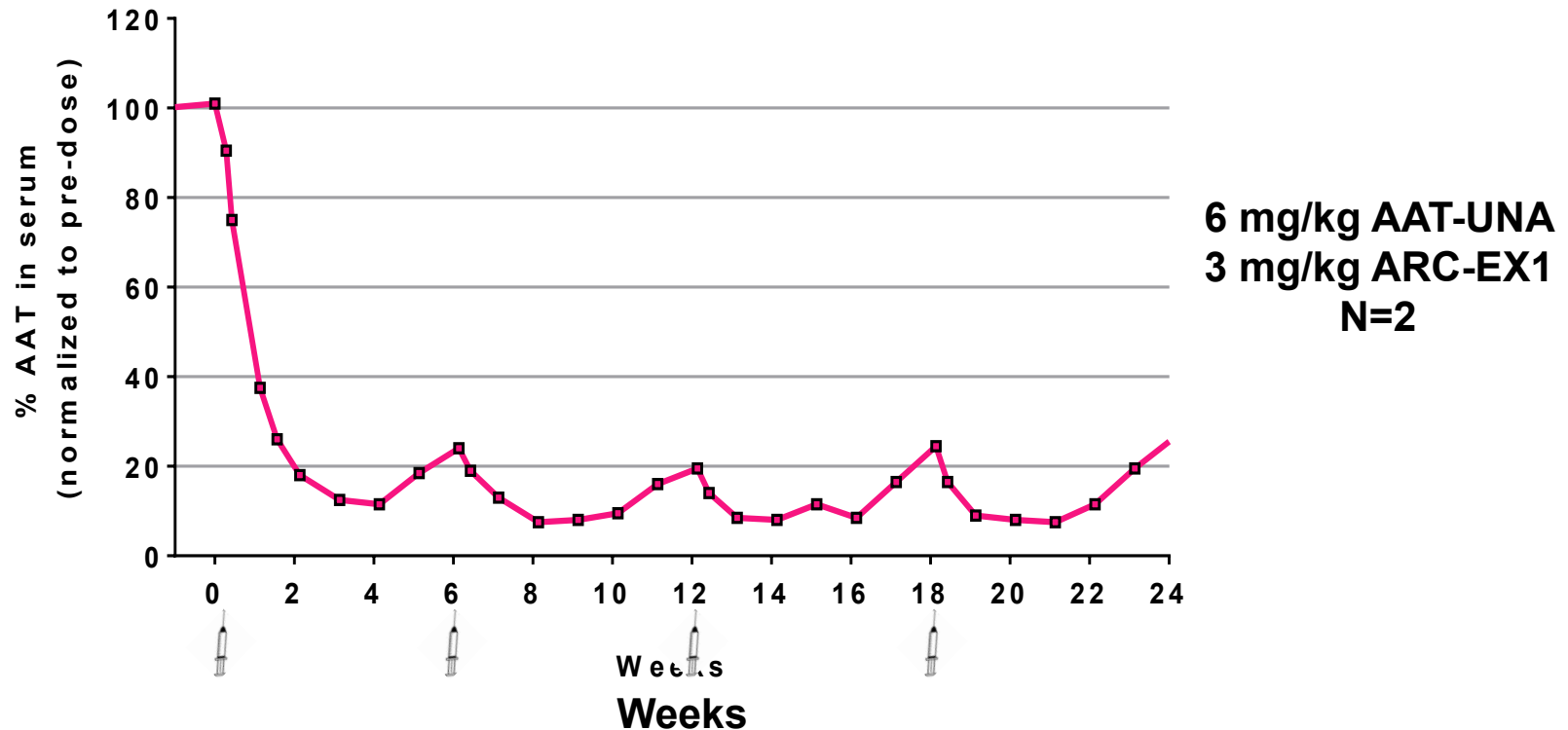
~90% reduction of serum AAT after first injection of ARC-AAT
Long duration of effect: ~80% reduction at 6 weeks
Sustained reduction of AAT with q6w dosing
Safety: no changes in clinical chemistry (ALT, AST, BUN, Creatinine)

ARC-AAT: Phase I clinical plan

- Single ascending dose P1 study ongoing in Australia

- Healthy volunteers and AATD patients

- **Primary Objectives:**

  - Determine the safety and tolerability of escalating doses of ARC-AAT

  - Evaluate the pharmacokinetics of different doses

- **Secondary Objectives:**

  - Evaluate the depth and duration of decline in serum total alpha-1 antitrypsin levels

  - Time for serum alpha-1 antitrypsin levels to return to baseline

- **Broad and powerful set of platforms led by DPC-enabled delivery**
  - Engineered endosomal escape enables deep KD

- **ARC-520 has lead in the clinic for novel treatment of HBV**
  - Well-tolerated antigen reduction in patients

- **ARC-AAT first pipeline expansion**
  - Clear unmet medical need for liver disease associated with AATD
  - De-risked by ARC-520: same DPC already showed well-tolerated KD

- **Deep Pipeline**
  - ARC-521 in the clinic in 2016
  - ARC-F12 in the clinic in 2016
  - ARC-LPa in the clinic in 2017
  - ARC-Hif2 in the clinic in 2017
  - Additional candidates coming

Thank you for your interest