RNA interference (RNAi) with ARC-AAT provides deep and prolonged knockdown of alpha-1 antitrypsin levels in healthy volunteers

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1. BACKGROUND

Alpha-1 antitrypsin deficiency (AATD)-associated liver disease

- Alpha-1 antitrypsin is a glycoprotein protease produced predominantly (~90%) by the liver and secreted into the serum.
- AATD is a genetic disorder causing pulmonary and liver disease.
- Most individuals with severe AATD are homozygotes for the PiZ allele (~1 in 3000 births in the U.S. are PiZZ).
- The PiZ mutation results in mis-folded protein (Z-AAT), formation of polymers, which can accumulate in hepatocytes and lead to fibrosis, cirrhosis and HCC while reducing secretion into blood.

ARC-AAT is a liver targeted RNAi therapeutic designed to stop Z-AAT production in the liver by silencing AAT gene with intent to:

- ***Prevent*** accumulation of disease-causing protein in liver
- ***Allow*** clearance of accumulated protein
- ***Prevent*** repeated cycles of cellular damage
- ***Reverse*** fibrosis associated with prior damage

Studies in transgenic PiZ mice, have shown reductions in AAT mRNA, serum Z-AAT levels and hepatocyte accumulation[1,2].

A Phase 1 study is being conducted in healthy volunteers (Part A) and AATD patients (Part B).

2. OBJECTIVES

Primary Objectives:

- Safety and tolerability of escalating single doses of ARC-AAT Injection
- Pharmacokinetics of ARC-AAT Injection
- Change in serum AAT following a single dose of ARC-AAT Injection

Multiple additional secondary and exploratory objectives.

Part A of the Phase 1 study is herein reported. The patient portion (Part B) of the trial is ongoing.

3. MATERIAL & METHODS

- Single-center (Part A) randomized, double-blind, placebo controlled, single-dose-escalation study.
- Healthy volunteers, age 18-50.
- 9 single-dose cohorts (2 placebo: 4 active) escalating from 0.3 to 8.0 mg/kg.
- Assessments include safety, PK, and change in serum AAT levels.
- Serum AAT levels were measured using nephelometry and turbidimetry.
- All subjects were followed until serum AAT returned to normal (> 90 mg/dL) or within 15% of baseline.

4. RESULTS

- Fifty-four subjects have been successfully dosed with 36 receiving drug and 18 receiving placebo.
- PK parameters were linear across dose levels with a constant half-life.
- Reductions in serum AAT of up to 90% were observed.
- A dose-response in serum AAT was observed.
- All serum AAT levels were > 90 mg/dL or returned to baseline within 100 days following a single dose.
- There have been no drop outs due to AEs, clinically significant changes in ECGs, DLCO or FEV_1 and one SAE in a placebo subject.
- The most frequently reported ARC-AAT Injection-related AEs was headache, nausea and rigor (each, 3 events in 36 [8%] subjects).
- No clinically significant transaminase (ALT, AST) elevations were reported.

Figure 1. Dose-response serum AAT reductions

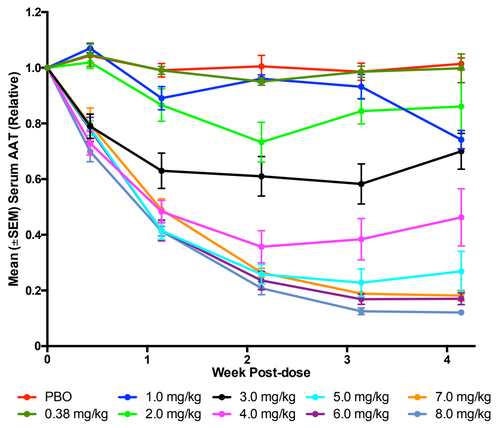
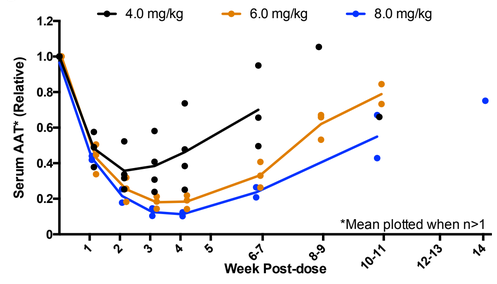


Figure 2. Serum AAT reduction duration



Dose Level (mg/kg)	3	4	5	6	7	8
Max KD	61.0%	76.1%	86.7%	87.1%	85.1%	89.8%
Mean Max KD ± SEM	45.3% ±6.8%	64.8% ±6.1%	78.1% ±4.4%	83.3% ±1.9%	82.6% ±1.3%	88.3% ±0.8%

Table 1. Treatment emergent adverse events at least possibly related to treatment

Adverse Event	Cohort 1 n = 4	Cohort 2 n = 4	Cohort 3 n = 4	Cohort 3b n = 4	Cohort 3c n = 4	Cohort 3d n = 4	Cohort 3e n = 4	Cohort 3f n = 4	Cohort 3g n = 4	Placebo n = 18	Active n = 36
Dose (mg/kg)	0.3	1	2	3	4	5	6	7	8		
Subjects reporting AEs (%)	1 (25%)	1 (25%)	2 (50%)	1 (25%)	2 (50%)	2 (50%)	1 (25%)	1 (25%)	3 (75%)	2 (11%)	14 (39%)
Total AE	1	1	2	2	5	3	1	1	5	2	21
Total SAE	0	0	0	0	0	0	0	0	0	0	0
Lethargy/Fatigue				1 mild					1 mild		
Headache		1 mild			1 mild	1 mild				1 mild	
Troponin Increased	1 mod										
URTI					1 mild						
Tachycardia			1 mod								
Nausea			1 mild		1 mild	1 mild					
Dizziness/lightheaded										1 mild	
Diarrhea				1 mod							
Dyspnea					1 mild						
Neutropenia					1 mild						
Back Pain						1 mild					
Chest Heaviness								1 mild			
Erythematous Skin Rash							1 mod				
Rigor									2 mod, 1 mild		
Infusion Reaction									1 mod		

5. CONCLUSION

Results from Part A of the Phase I study indicate that ARC-AAT Injection is well-tolerated and provides deep and durable knockdown of hepatic AAT production. AATD patient dosing is underway.

Duration of effect indicates that monthly, or less frequent, dosing is likely.

ACKNOWLEDGEMENTS

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REFERENCES

1. Wooddell (2015) IBC's 17th Annual TIDES Conference, oral presentation.
2. Wooddell (2016) The Liver Meeting, Parallel F, Session 19 oral presentation #124.

DISCLOSURES

- **Alice Turner** – ARC, Grifols, Alpha-1 Foundation (Grant)
- **James Hamilton**, **Bruce D. Given**, **Dawn R Christianson** - Arrowhead Pharmaceuticals Inc. (ARC) (Employment)
- **Rohit Loomba** - Galmed Inc, Tobira Inc, ARC (Advisory Committee (AC) or Review Panels (RP)); Gilead Inc, Corgenix Inc, Janssen and Janssen Inc, Zafgen Inc, Celgene Inc, Alnylam Inc, Inanta Inc, Deutrx Inc (Consulting); Daiichi Sankyo Inc, AGA, Merck Inc, Promedior Inc, Kinemed Inc, Immuron Inc, Adheron Inc (Grant)
- **James Stoller** - Grifols, COPD Foundation, ARC (AC or RP); Alpha-1 Foundation (Board Member); ARC, CSL Behring, Baxalta (Consulting); CSL Behring (Grant)
- **Jeffrey Teckman** – ARC (AC); Dicerna, Ionis Pharmaceuticals, Genkyotex, The Alpha-1 Project, RxCelerate, Editas, Intelia, AstraZenica (Consulting); Alnylam, ARC, Alpha-1 Foundation, Gilead (Grant)
- **Jonathan G. Burdon** –Commonwealth Serum Laboratories (Consulting, AC); ARC (Data Safety Committee)
- **Robert Bals** - AstraZeneca, GSK, Boehringer Ingelheim (AC); Schwiete-Foundation, DFG, BMBF (Grant)
- The following people have nothing to disclose: **Jason Lickliter, Jan Stolk**