Hepatic targeted RNA interference provides deep and prolonged knockdown of alpha-1 antitrypsin levels in ZZ patients

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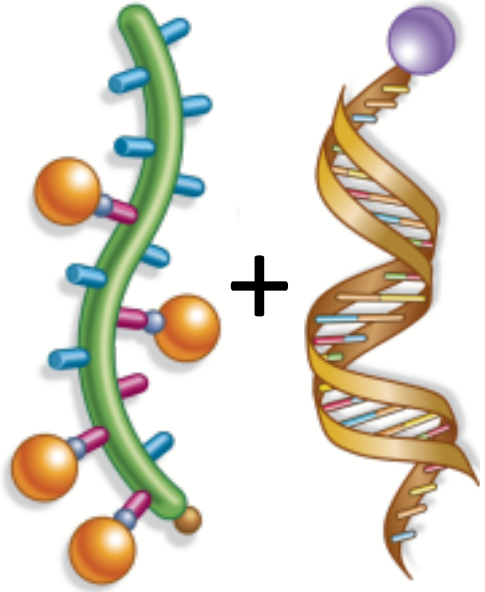
19-23 APRIL, AMSTERDAM, THE NETHERLANDS

Disclosures

- **A. Turner:** Grant: Arrowhead Pharmaceuticals, Alpha-1 Foundation
- **J. Stolk:** None Declared
- **R. Bals:** Grant: Schwiete-Foundation, DFG, BMBF, Advisory Committee: AstraZeneca, GSK, Boehringer Ingelheim
- **J. Lickliter:** None Declared
- **J. Hamilton, D. Christianson, B. Given:** Employed at Arrowhead Pharmaceuticals
- **J. Burdon:** Consultant: Commonwealth Serum Laboratories, Data Safety Committee: Arrowhead Pharmaceuticals
- **R. Loomba:** Grant: Adheron, BMS, Daiichi-Sankyo Inc., Galectin, Galmed, GE, Genfit, Gilead, Immuron, Intercept, Kinemed, Madrigal, Merck, NGM, Promedior, Prometheus, Siemens, Tobira, Consultant: Alnylam, Bird Rock Bio, BMS, Boehringer Ingleheim, Celgene, Conatus, DeuteRx, Eli Lily, Enanta, Fibrogen, Genkyotex, Gilead, GRI Bio, ISIS, Janssen Inc. Kirin, Madrigal, Metacrine, NGM, Nitto Denko, Pfizer, Receptos, Roivant, RuiYi, Sanofi, Scholar Rock, Shire, Tasly, Viking, Yuhan Pharmaceuticals, Zafgen, Advisory Committee: Arrowhead Research, Conatus, Galmed, Gilead, Intercept, NGM, Nimbus, Octeta, Tobira; Co-Founder: Liponexus Inc,
- **J. Stoller:** Grant: CSL Behring, Consultant: Arrowhead Pharmaceuticals, CSL Behring, Shire, Advisory Committee: Grifols, COPD Foundation, Alpha-1 Foundation
- **J. Teckman:** Grant: Alnylam, Arrowhead Pharmaceuticals, Alpha-1 Foundation, Gilead, Consultant: Dicerna, Ionis Pharmaceuticals, Genkyotex, The Alpha-1 Project, RxCelerate, Editas, Intelia, AstraZeneca

ARC-AAT: an siRNA Therapeutic



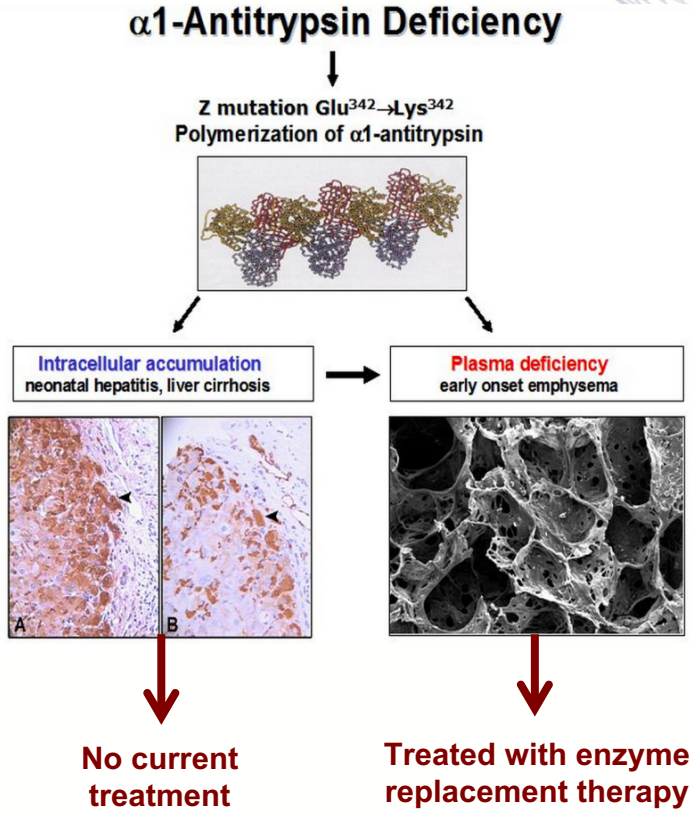
EX1 and cholesterol-linked RNAi trigger

ARC-AAT Consists of:

- Polymer delivery system (EX1)
- Liver targeted siRNA
- Mixed in pharmacy and co-administered via IV infusion
- ARC-AAT uses 2:1 ratio of siRNA to EX1, 4 mg/kg means 4 mg/kg RNAi trigger, 2 mg/kg EX1 delivery system

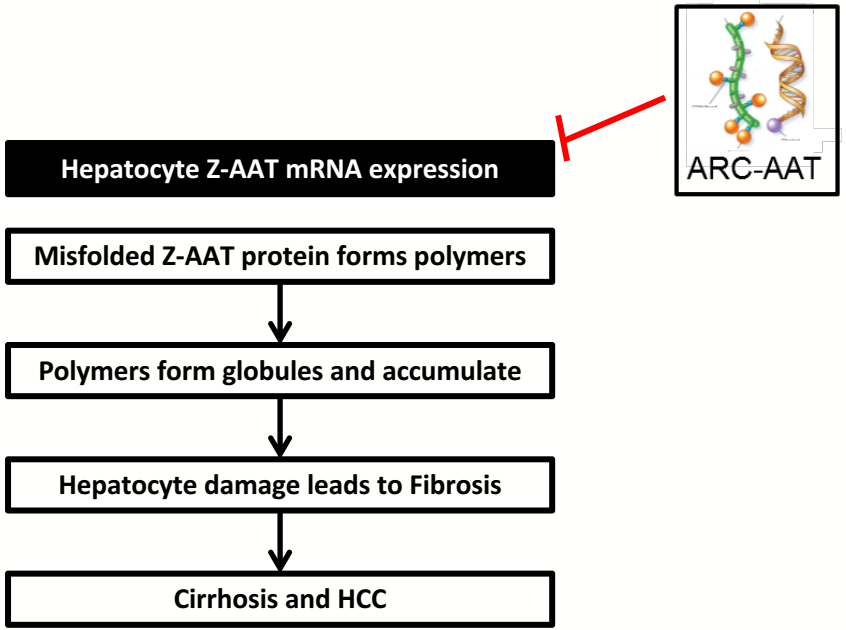
Alpha-1 Antitrypsin Deficiency (AATD)

- Alpha-1 antitrypsin: glycoprotein protease produced predominantly (~90%) in liver and secreted into blood.
- Primary AAT function is to inhibit lung neutrophil elastases.
- Severe AATD due to mutant AAT that is misfolded, poorly secreted from cells = serum deficiency (pulmonary disease) + liver storage disease.
- ~96% of the clinical disease is from Z-mutant homozygosity (PiZZ)

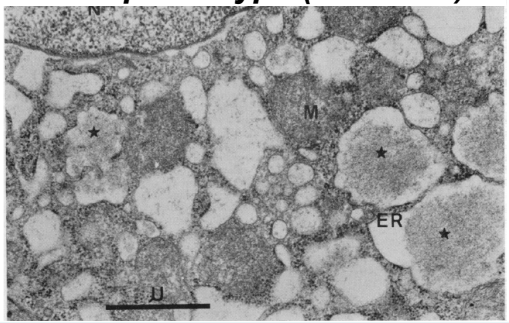


Janciauskiene, et al. 2013 *Acute Phase Proteins*

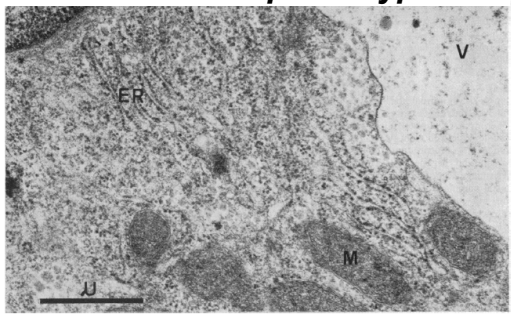
Therapeutic Rationale for ARC-AAT in AATD Liver Disease



PiZZ phenotype (diseased)



Pi-null liver phenotype



Feldmann, G., et al. (1975) *Gut*

ARCAAT-1001 Phase 1 Design

- **Part A**, Single dose NHV study
  - Conducted in Australia
  - 9 escalating dose cohorts, 6 per cohort (4 active 2 placebo)
  - Single dose, follow serum AAT, PK, safety parameters (labs, ECG, PFTs) through Day 29
  - Dose escalation 0.38 to 8.0 mg/kg
  - All subjects were followed until AAT returned to normal (> 90 mg/dL) or within 15% of baseline

- Initiated Part B in AATD patients based on KD of 30% in 3 of 6 in a Part A cohort

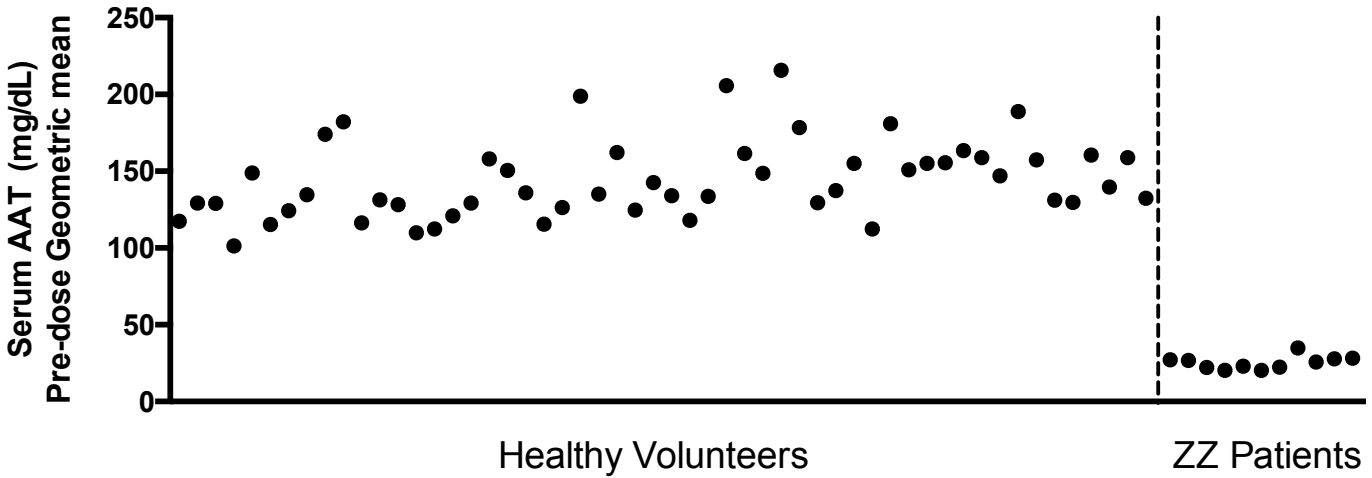
- **Part B**, single doses in AATD patients
  - Multiple sites - Australia, UK, Germany, Netherlands
  - 6 per cohort (4 active 2 placebo)
  - Planned for single escalating dose cohorts at 2, 4, 6 mg/kg
  - All patients were followed until AAT returned to within 15% of baseline

ARCAAT-1001 Patient Enrollment Criteria

- Key patient (Part B) inclusion criteria
  - 18-70 years old
  - PiZ phenotype or PiZZ genotype (all were ZZ)
  - Non-smoker for at least 3 years

- Key patient (Part B) exclusion criteria
  - ALT or AST > 3X ULN
  - FEV_1 at Screening < 60% predicted
  - Liver elastography (i.e. FibroScan®) > 11 kPa at Screening

Part A & B Baseline Serum AAT Levels



Serum AAT Baseline (mg/dL)		
	HV (n=54)	ZZ (n=11)
Average	144.7	25.5
SD	27.28	4.82
Maximum	222.3	36.8
Minimum	94.0	16.9

NHV Demographics & Characteristics

Characteristic	Active (all cohorts)	Placebo
Number	36	18
Mean Age	29.2	25.4
Median Age	27.0	24.0
Male	15	6
Female	21	12
BMI (mean)	23.2	23.38
Mean (SD) baseline serum AAT (mg/dL)	144.7 (27.28) Range: 94.0-222.3	

Healthy Volunteer Results

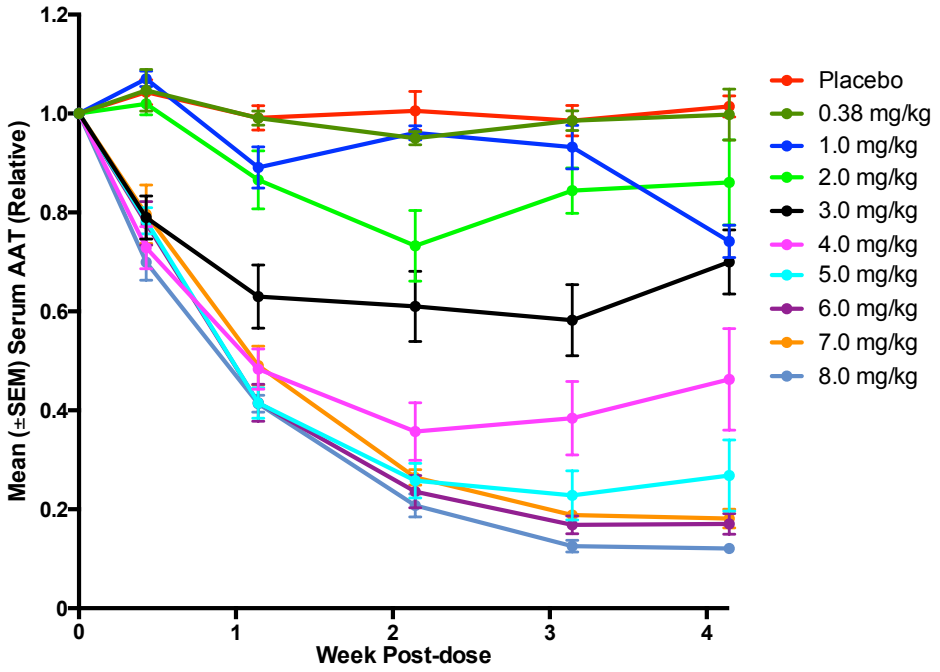
- 54 NHV subjects enrolled in Part A
- Maximum serum AAT reduction of **89.8%** observed with well defined dose response
  - Serum AAT variability 9.1% in NHV placebo group
- All AAT levels returned to baseline (or above 90 mg/dL) within 100 days after single dose
- No drop outs due to AEs; no clinically significant changes in safety labs, ECGs, DLCO or FEV1
  - one SAE (rhabdomyolysis) in a placebo subject
- The most frequently reported AEs in subjects receiving ARC-AAT were headache (19%), URTI (14%), nausea (8%) and chills (8%)

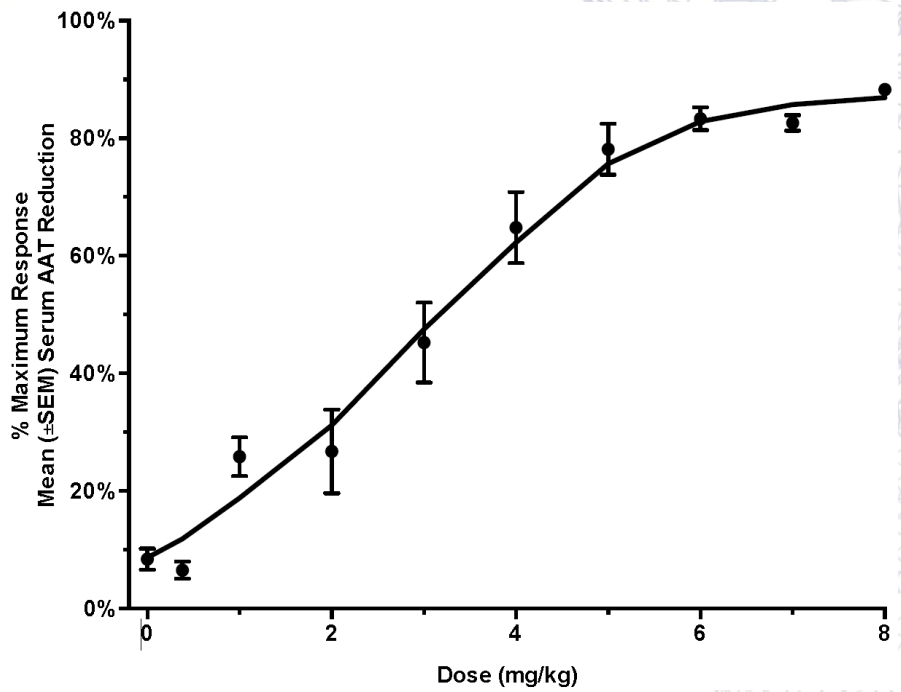
Part A treatment emergent adverse events (reported >1 subject)

Adverse Event (Medra Preferred Term)	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		
Headache	1	1			1	2	2			0	7(19%)
Muscle Spasm		1	1							0	2(6%)
URTI					2	1		1	1	1(6%)	5(14%)
Nasopharyngitis										2(11%)	0
Nausea			1		1	1				0	3(8%)
Dizziness										2(11%)	0
Fatigue				1					1	1(6%)	2(6%)
Chills									3	0	3(8%)
Dysmenorrhea								1	1	0	2(6%)

- No Severe AEs in subjects receiving ARC-AAT. All AEs mild or moderate
- No clear pattern of increase in number of or severity of AEs with dose escalation
- Symptoms consistent with infusion reaction more common at highest dose
- All AEs considered possibly related to treatment were reported at The Liver Meeting, November 2016

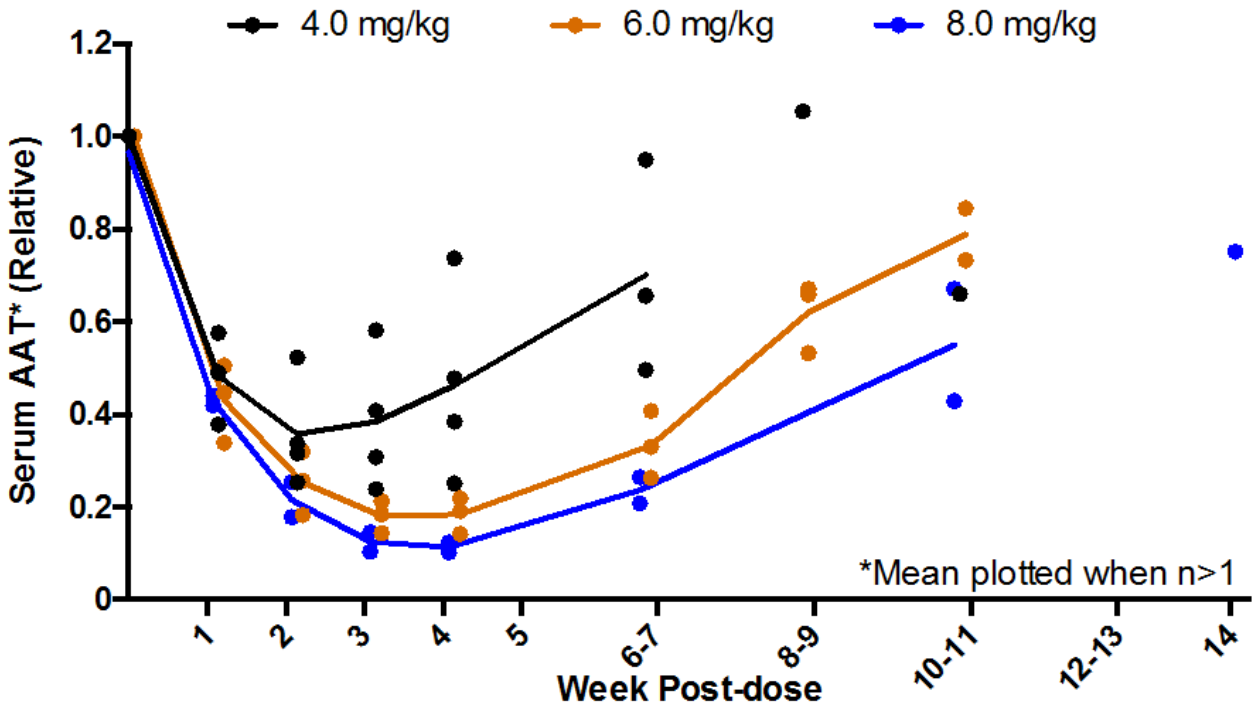
Healthy Volunteer AAT Levels - Dose Response Evident





Dose Level (mg/kg)	PBO (n=18)	0.38 (n=4)	1 (n=4)	2 (n=4)	3 (n=4)	4 (n=4)	5 (n=4)	6 (n=4)	7 (n=3)	8 (n=3)
Max KD	24.8%	9.3%	31.9%	36.3%	61.0%	76.1%	86.7%	87.1%	85.1%	89.8%
Mean Max	8.4%	6.6%	25.9%	26.7%	45.3%	64.8%	78.1%	83.3%	82.6%	88.3%
P value	N/A	0.6363	0.0004	0.0014	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Healthy Volunteer AAT Levels – Duration of Reductions Increase with Dose



Part B: Patient Demographics & Characteristics

Characteristic	Active (all cohorts)	Placebo
Number	7	4
Mean Age	61.3	58.8
Median Age	60	61.5
Male	3	1
Female	4	3
BMI (mean)	26	26.4
Mean (SD) baseline serum AAT (mg/dL)	25.46 (4.82) 16.9-36.8	

AATD Patient Results

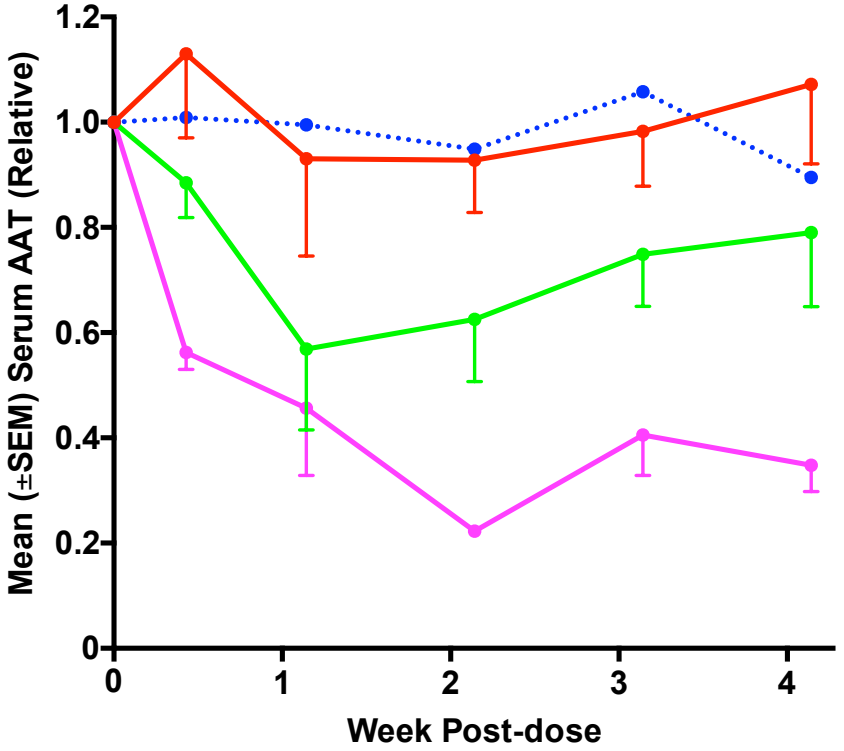
- 11 PiZZ patients enrolled in Part B (7 active, 4 placebo)
  - 3 received 2.0 mg/kg, 1 received partial dose of 1.0 mg/kg
  - 3 received 4.0 mg/kg
- Maximum AAT reduction of 78.8% observed at 4.0 mg/kg
  - Serum AAT variability in placebo 23.2%
- All AAT levels returned to baseline within 100 days following a single dose.
- There were no SAEs, patient drop outs due to AEs, clinically significant changes in labs, ECGs, DLCO or FEV1 - all AEs mild or moderate

All reported treatment emergent AEs in AATD Patients

Adverse Event (Medra preferred term)	Cohort 4 n = 4	Cohort 5 n = 3	Placebo n = 4	Active n = 7
Dose (mg/kg)	2.0	4.0		
Subjects reporting AEs (%)	3(75%)	2(50%)	4 (100%)	5(71%)
Total AE	7	4	8	11
Total SAE	**0**	**0**	**0**	**0**
Asthma	1		0	1(14%)
URTI			1(25%)	0
Peripheral Edema			1(25%)	0
Paresthesia	1		0	1(14%)
Headache	1		1(25%)	1(14%)
Nausea	1		0	1(14%)
Pyrexia	1		0	1(14%)
Feeling cold	1		0	1(14%)
Peripheral coldness	1		0	1(14%)
Muscular weakness		1	0	1(14%)
Cough		1	1(25%)	1(14%)
Migraine		1	0	1(14%)
Fatigue			1(25%)	0
Dyspnea			1(25%)	0
Oropharyngeal pain			1(25%)	0
Diarrhea		1	0	1(14%)
Back pain			1(25%)	0

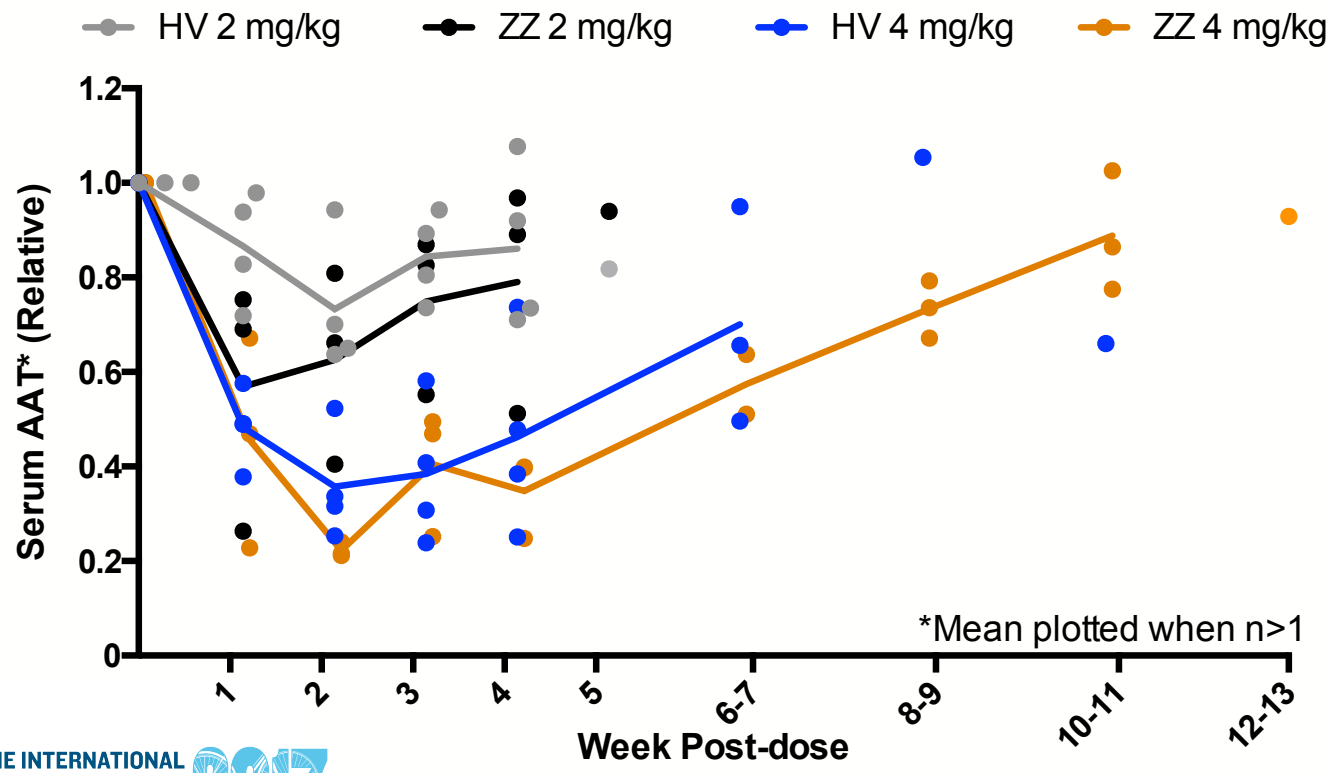
- No pattern of increase in number or severity of AEs with dose escalation
- No pulmonary AEs in patients receiving ARC-AAT
- All AEs mild or moderate

Patient AAT Results Again Show Dose Response



Dose Level (mg/kg)	PBO (n=4)	2 (n=3)	4 (n=3)
Max KD	46.6%	73.7%	78.8%
Mean Max KD ± SEM	21.9% 9.80%	44.1% 15.00%	78.1% 0.48%
P value	N/A	0.2524	0.0047

Patients and NHVs Show Similar Depth and Duration of AAT Knockdown at Same Dose



Conclusions

- ARC-AAT was well tolerated in NHVs and patients with AATD
- Single doses of ARC-AAT resulted in dose – related knockdown of AAT, reaching maximum approaching 90% with 6-8 mg/kg in NHVs
- ARC-AAT at doses of 2 and 4 mg/kg produced similar knockdown in NHVs and AATD patients
- ARC-AAT program was terminated in late 2016 due to findings in a chronic NHP study involving an HBV drug (ARC-521) using the same EX1 delivery system.
  - EX1 polymer common amongst all clinical stage drug candidates including ARC-AAT
  - EX1 was determined to be the cause of toxicity in the NHP study
- Sponsor is developing ARO-AAT, a subcutaneously administered RNAi drug that does not use EX1.