ARO-AAT reduces serum and intra-hepatic Z-AAT protein in PiZZ alpha-1 antitrypsin deficient patients with liver disease leading to improvements in clinically relevant liver biomarkers

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INTRODUCTION

Homozygous PiZZ alpha-1 antitrypsin deficiency (AATD) is an autosomal co-dominant genetic disorder causing pulmonary and liver disease in children and adults. Normally, wild type alpha-1 antitrypsin (AAT) is synthesized by hepatocytes and secreted into the circulation principally to protect the lung during inflammation by inhibition of neutrophil proteases. In AATD, the mutant Z protein (Z-AAT) misfolds and accumulates in hepatocytes. This triggers liver injury which can lead to cirrhosis and the reduced serum activity can lead to lung injury. Intracellular proteolysis pathways are activated in hepatocytes to reduce Z-AAT accumulation, but this may prove insufficient with resultant liver injury in some individuals. ARO-AAT is a hepatocyte targeted RNAi therapeutic designed to silence expression of Z-AAT mRNA leading to reduced Z-AAT protein synthesis. Herein, we report initial results from Cohort 1 in the AROAAT2002 phase 2 clinical trial.

AIM

To evaluate the safety and pharmacodynamic effects of ARO-AAT on clinically relevant biomarkers of liver disease in homozygous PiZZ patients with evidence of liver fibrosis.

METHODS

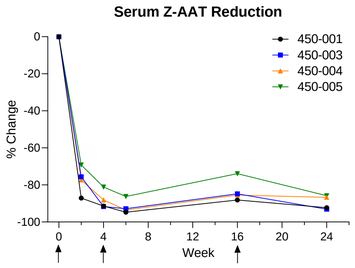
- Study Design: Cohort 1, open-label, n=4
  - 200 mg ARO-AAT administered subcutaneously on Wk 0, Wk 4, Wk 16
  - Liver biopsy performed at screening and at Wk 24
  - PiZZ patients, age 18-65 with evidence of fibrosis (F2-F3) at screening
- Assessments: Safety (including pulmonary function tests), changes in serum Z-AAT, Liver Z-AAT, Pro-C3, Liver Elastography (FibroScan®)
  - Serum and Liver Z-AAT protein were measured using a validated bioanalytical method
  - Liver globule assessment was done semi-quantitatively on PAS+D staining at baseline and 24 weeks by a single liver histopathologist. Portal tract involvement, periportal hepatocyte involvement, and zonal location were each given a score ranging from 0-3 and then summarized as a total score from 0-9: Portal tract and periportal hepatocyte involvement were each scored: 1=<1/3, 2=1/3-2/3, 3=>2/3; Zonal location: 1=Zone 1, 2=Zone 1 & 2, 3=all Zones or only 2 & 3
  - Additional histologic adjudication is ongoing.
- All subjects have continued into the 1-year extension study
- Data Cut: Safety 2 October 2020; All other assessments 7 July 2020

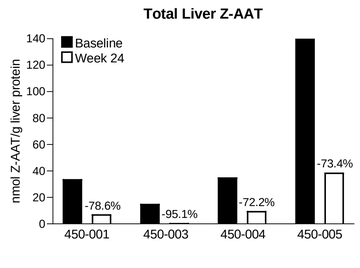
RESULTS

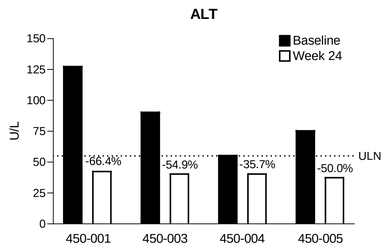
Cohort 1 Baseline Characteristics

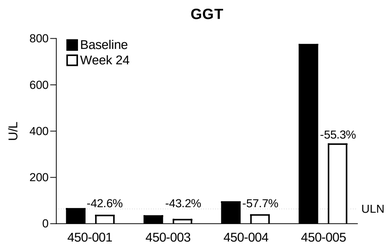
	Subject			
	450-001	450-003	450-004	450-005
Age (years)	46	20	56	56
BMI (kg/m2)	24.6	23.5	26.3	30.7
Liver Fibrosis (Biopsy)	F3	F2	F2	F3
FEV1 % predicted	56%	87%	106%	106%
AAT Augmentation (Y/N)	Y	N	N	N

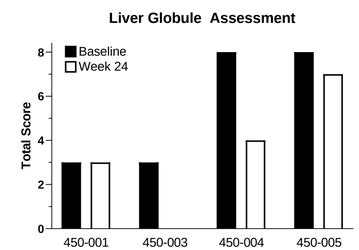
*Screening assessment







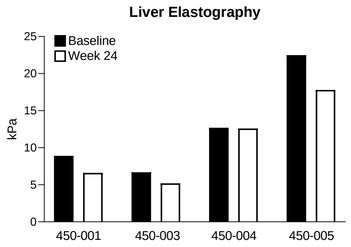




Pharmacodynamic Response at Week 24 Relative to Baseline

	Subject			
	450-001	450-003	450-004	450-005
Serum Z-AAT, Δ %	-92.3%	-93.1%	-86.7%	-85.8%
Total liver Z-AAT*, baseline	33.9	15.2	35.2	146
Week 24	7.25	0.751	9.77	38.8
Δ %	-78.6%	-95.1%	-72.2%	-73.4%
Soluble liver Z-AAT* baseline	16.8	13.6	33.3	33.5
Week 24	1.71	0.697	4.38	6.3
Δ %	-89.8%	-94.9%	-86.8%	-81.2%
Insoluble liver Z-AAT* baseline	17.1	1.6	1.9	112.5
Week 24	5.54	0.054	5.39	32.5
Δ %	-67.6%	-96.6%	183.7%	-71.1%
ALT, U/L, baseline	128	91	56	76
Week 24	43	41	36	38
Δ %	-66.4%	-54.9%	-35.7%	-50.0%
GGT, U/L, baseline	68	37	97	777
Week 24	39	21	41	347
Δ %	-42.6%	-43.2%	-57.7%	-55.3%
FibroScan®, kPa, baseline	8.9	6.7	12.7	22.5
Week 24	6.6	5.2	12.6	17.8
Δ %	-25.8%	-22.4%	-0.8%	-20.9%
Pro-C3, ng/mL, baseline	38.3	16.4	22.3	23.6
Week 24	18.6	17.3	15.4	15.2
Δ %	-51.4%	5.5%	-30.9%	-35.6%

*nmol/g liver protein



Pulmonary Function Overtime (FEV1pp)

Subject	Baseline	Wk4	Wk16	Wk24
450-001	56.0	51.0	55.0	52.0
450-003	87.0	83.0	84.0	78.0
450-004	106.0	106.0	107.0	108.0
450-005	106.0	98.0	101.0	104.0

RESULTS

Safety

- Overall, ARO-AAT 200 mg as a subcutaneous injection was well tolerated in PiZZ AATD subjects
- One treatment emergent SAE of Epstein bar virus related myocarditis was reported
- No treatment emergent AEs related to change in pulmonary status or pulmonary function were reported
- No clinically meaningful changes in ppFEV1 from baseline to Week 24 were observed

Pharmacodynamic Response at 24 weeks:

- Serum Z-AAT reductions were 86-93%
- Total intra-hepatic Z-AAT reductions were 72-95%.
- All patients demonstrated >80% reduction in liver Z-AAT monomer (soluble)
- 3 of 4 patients demonstrated reductions in Z-AAT polymer (insoluble) with a range of 68-97%
- 3 of 4 subjects had a decrease in liver globule involvement and 1 subject remained unchanged
- All patients showed reductions in ALT and in GGT
- Baseline to Week 24 ALT reductions ranging from 36-66%
- Baseline to Week 24 GGT reductions ranging from 43-58%
- 3 of 4 patients demonstrated a substantial reduction in FibroScan® score
- 3 of 4 patients showed greater than 30% reduction in serum Pro-C3, a marker of fibrogenesis

CONCLUSIONS

In this small cohort of n=4, 3 doses of ARO-AAT 200 mg, over 24-weeks, resulted in consistent reductions of the disease-causing Z-AAT protein and improvements in clinically relevant biomarkers of liver disease.

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Clinicaltrials.gov identifier: NCT03946449

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