ARO-AAT Treatment Reduces Intra-hepatic Z-AAT Leading to Improved Parameters of Liver Health and Fibrosis Regression

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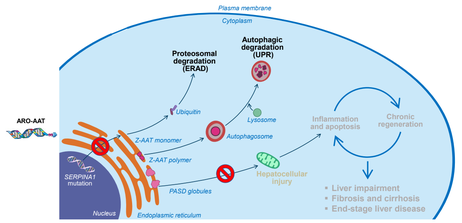
INTRODUCTION

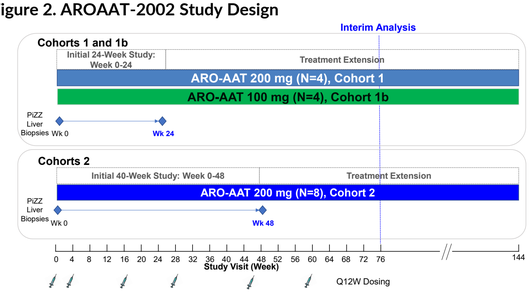
- Homozygous PiZZ alpha-1 antitrypsin deficiency (AATD) is a rare and serious disease caused by mutation in the *SERPINA1* gene that leads to loss-of-function pulmonary disease and gain of-function liver disease.
- In the liver, the PiZZ allele produces misfolded and poorly secreted AAT protein (Z-AAT), leading to mutant Z-AAT accumulation that causes ER stress, hepatocellular injury, inflammation, and apoptosis.
- Over time, AATD-associated liver disease can progress to fibrosis, cirrhosis, hepatocellular carcinoma, and end-stage liver disease.
- ARO-AAT is a hepatocyte-targeted RNAi therapeutic designed to silence expression of Z-AAT mRNA leading to reduced Z-AAT protein synthesis (Figure 1).

Figure 1. Proposed ARO-AAT Mechanism of Action



METHODS

Figure 2. AROAAT-2002 Study Design



Data Cut: 31 August 2021

- Assessments: Safety, serum Z-AAT, liver Z-AAT, Pro-C3, liver enzymes, liver stiffness (FibroScan®), histology (PAS+D and METAVIR fibrosis)
- Histology was assessed and adjudicated by 3 pathologists blinded to subject and time point.
- PAS+D globule burden was assessed for extent of portal tract and periportal hepatocyte involvement and zonal location (score 0-9).

RESULTS

Table 1. Baseline Characteristics

	ARO-AAT 200 mg Cohort 1 (N=4)	ARO-AAT 200 mg Cohort 2 (N=8)	ARO-AAT 100 mg Cohort 1b (N=4)	Total (N=16)
Mean age (SD), years Min, Max	45 (17) 20, 56	55 (14) 24, 66	55 (10) 41, 65	52 (14) 20, 66
Male, n (%)	4 (100%)	7 (88%)	3 (75%)	14 (88%)
Mean weight (SD), kg	87 (14)	77 (14)	83 (17)	81 (14)
Mean BMI (SD), kg/m^2	26.3 (3.2)	24.1 (4.7)	27.5 (4.1)	25.5 (4.2)
Genotype (PiZZ-positive)	4 (100%)	8 (100%)	4 (100%)	16 (100%)
Fibrosis Stage F0 F1 F2 F3 F4 Not evaluable	 0 (0%) 0 (0%) 1 (25%) 1 (25%) 2 (50%) 0 (0%)	 0 (0%) 1 (13%) 3 (38%) 3 (38%) 0 (0%) 0 (0%)	 1 (25%) 1 (25%) 1 (25%) 0 (0%) 0 (0%) 1 (25%)	 1 (6%) 2 (13%) 5 (31%) 4 (25%) 2 (13%) 1 (6%)
Mean FEV1 Percent Predicted (SD)	88 (25)	76 (18)	101 (22)	85 (22)
On AAT Augmentation Therapy	1 (25%)	4 (50%)	1 (25%)	6 (38%)

Table 2. ARO-AAT Treatment Allows Clearance of Liver Z-AAT Protein[a]

Median (Range) % Change	ARO-AAT 200 mg Cohort 1 (N=4)	ARO-AAT 200 mg Cohort 2 (N=8)	ARO-AAT 100 mg Cohort 1b (N=4)
Total Liver Z-AAT			
Week 24/48	**-76%** (-95, -72) (n=4)	**-90%** (-100, -77) (n=6)	**-83%** (-89, -76) (n=4)
Soluble Liver Z-AAT			
Week 24/48	**-88%** (-95, -81) (n=4)	**-92%** (-99, -79) (n=6)	**-86%** (-90, -79) (n=4)

[a] nmol/g total protein

Table 3. ARO-AAT Treatment Improved Liver Fibrosis

	ARO-AAT 200 mg Cohort 1 (N=4)	ARO-AAT 200 mg Cohort 2 (N=8)	ARO-AAT 100 mg Cohort 1b (N=4)
≥1-point Improvement from Baseline to Week 24 or 48	2/4 (50%)	4/7 (57.1%) [a]	0/3 (0%) [b]
No Change from Baseline to Week 24 or 48	2/4 (50%)	1/7 (14.3%)	3/3 (100%)
≥1-point Worsening from Baseline to Week 24 or 48	0/4 (0%)	2/7(28.6%)	0/3 (0%)

[a] At data cutoff, one subject in Cohort 2 had not yet reached Wk48 and was not included in the analysis
[b] One subject in Cohort 1b had baseline biopsy that was not evaluable for METAVIR fibrosis

- Two patients in Cohort 2 had an increase from F2 to F3, although both had profound reduction in PAS+D globule burden and reduced ALT and GGT after treatment.
  - One subject had a maximum globule burden score of 9 at baseline and 0 at Week 48
  - The other subject had a score of 4 at baseline and 0 at Week 48

Figure 3. ARO-AAT Treatment Reduced Serum Z-AAT Protein

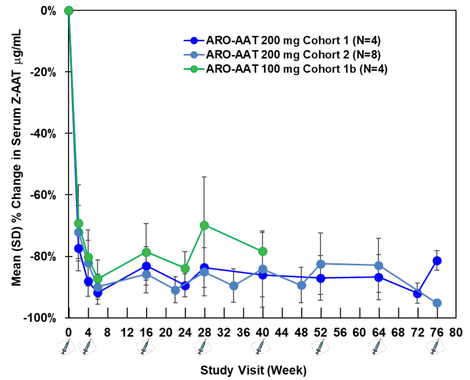
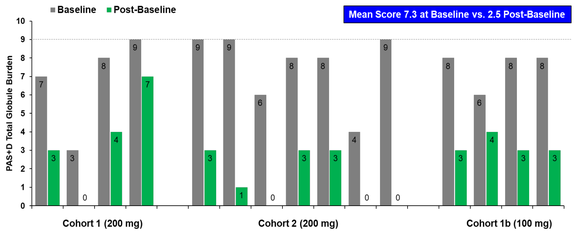
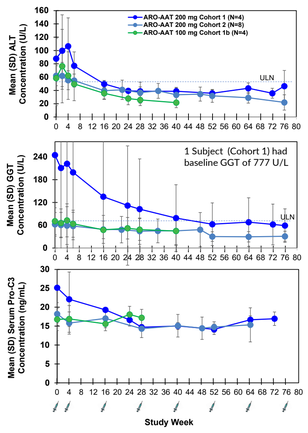


Figure 4. ARO-AAT Treatment Reduced Histological Globule Burden



Postbaseline = Last observation at Week 24 or 48

Figure 5. ARO-AAT Treatment Improved Biomarkers of Liver Health



RESULTS

Table 4. Summary of Safety and Adverse Events

Subject Incidence, n (%)	ARO-AAT 200 mg (N=12)	ARO-AAT 100 mg (N=4)	All (N=16)
Treatment-emergent AEs (TEAEs)	11 (92%)	4 (100%)	15 (94%)
TEAEs in 3 or more subjects			
Blood CK increased	3 (25%)	1 (25%)	4 (25%)
Back pain	2 (17%)	1 (25%)	3 (19%)
Diarrhea	3 (25%)	0 (0%)	3 (19%)
Dizziness	1 (8%)	2 (50%)	3 (19%)
Dyspnea	2 (17%)	1 (25%)	3 (19%)
Headache	2 (17%)	1 (25%)	3 (19%)
Nasopharyngitis	2 (17%)	1 (25%)	3 (19%)
Treatment-related TEAEs	6 (50%)	3 (75%)	9 (56%)
Serious TEAEs	4 (33%)	0 (0%)	4 (25%)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	0 (0%)	0 (0%)	0 (0%)
TEAEs causing deaths	0 (0%)	0 (0%)	0 (0%)

- No treatment emergent AEs related to change in pulmonary status or pulmonary function were reported.
- No clinically meaningful changes in ppFEV1 from baseline (mean 85% [N=16]) were observed at Week 40 (mean 81% [N=15]) or at Week 72 (mean 84% [N=4]).
- Four SAEs were reported: EBV-related myocarditis, diverticulitis, dyspnea, and vestibular neuronitis, all of which involve confounding factors or alternative etiology.

CONCLUSIONS

- ARO-AAT reduced serum and liver Z-AAT and globule burden in all patients and normalized liver enzymes.
- These data demonstrate that removal of the causative factor, Z-AAT, in AATD liver disease ameliorates liver injury, and can lead to an improvement in fibrosis.

ACKNOWLEDGEMENTS

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Clinicaltrials.gov identifier: NCT03946449

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