Emerging Therapies for AAT Liver Disease

ARO-AAT-2002 Clinical Data Review

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Accumulation of Hepatotoxic Z-AAT Protein Causes Liver Disease in Alpha-1 Antitrypsin Deficiency (AATD)

Circulating AAT → Lung

- Proteosomal degradation (ERAD)
- Autophagic degradation (UPR)

Wild-type AAT → Z-AAT monomer → Z-AAT polymer

- Ubiquitin
- Lysosome
- Autophagosome
- Mitochondrial and redox injury
- PASD globules

SERPINA1 Mutation

- Nucleus
- Endoplasmic reticulum

- Chronic regeneration
  - Liver impairment
  - Fibrosis and cirrhosis
  - End-stage liver disease

Inflammation and apoptosis
RNAi as Therapeutic Approach to Silence Protein Expression
Targeted RNA Interference Molecule (TRiM™)

- ARO-AAT: A Hepatocyte Targeted RNAi Molecule to Silence Hepatocyte AAT Synthesis

- Arrowhead's TRiM™ Platform:
  - **Targeted**: designed to deliver drug to cells in the liver
  - **Precise**: small interfering RNA molecules (RNAi triggers) designed to silence specific gene of interest and prevent protein synthesis
  - **Efficient**: uses natural cellular mechanism
ARO-AAT Clinical Development Program Overview

On October 8, 2020, Arrowhead Pharmaceuticals and Takeda entered into an agreement to co-develop ARO-AAT.

- Arrowhead will continue to conduct the Phase 2 studies through completion.
  - The primary analysis of AROAAT2001 at Week 16 is intended to enable End of Phase 2 meeting with FDA.
  - Dose selection based on AROAAT2001 results will be used in subsequent Phase 3 study.
- Takeda will design and conduct the Phase 3 study in collaboration with Arrowhead.

AROAAT2001
Phase 2, Randomized, Placebo-Controlled Study (Planned N=36)

AROAAT2002
Phase 2, Open-label Study (Actual N=16)

End of Phase 2 Meeting

AROAAT3001
Phase 3, Randomized, Placebo-controlled Study (Planned)
Clinically Relevant Endpoints in ARO-AAT Studies

Genetic Mutation
- PiZZ Homozygosity
  - Liver Z-AAT Monomers
  - Liver Z-AAT Polymers
  - Globules
  - Circulating AAT Protein

Accumulation and Impaired Clearance of Mutant Z-AAT Protein

Hepatic Impairment
- Fibrosis
- Inflammation
- Biomarkers of Liver Injury

Evaluations (Endpoints)
- METAVIR Fibrosis Score
- Fibroscan
- Portal Inflammation
- Interface Hepatitis
- Liver Enzymes (ALT, GGT)
- Serum Pro-C3
- Serum Z-AAT
- Liver Z-AAT
- PAS+D Globules
AROAAT-2002 Study Design

Endpoints
- Serum Z-AAT and liver Z-AAT (total, monomer, polymer)
- Adjudicated Histology
  - PAS+D Globules
  - METAVIR fibrosis score
- Serum ALT, GGT, FibroScan, Pro-C3
- Treatment-emergent AEs (TEAEs), SAEs

Interim Analysis
PD & Efficacy
- All 9 subjects on 200 mg:
  - Cohort 1 (n=4): 24-week biopsy and 48-week lab
  - Cohort 2 (n=5): 48-week biopsy and 52-week lab

Safety
- All 16 subjects (median follow up of 60 weeks for 200 mg dose and 16 weeks for 100 mg dose)
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Median (min, max) or n (%)</th>
<th>Cohort 1 (n=4)</th>
<th>Cohort 2 (n=5)</th>
<th>Total (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>51 (20,56)</td>
<td>62 (50,66)</td>
<td>56 (20,66)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>4 (100%)</td>
<td>4 (80%)</td>
<td>8 (89%)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>86 (71, 104)</td>
<td>84 (63, 105)</td>
<td>84.5 (63, 105)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 (23.5, 30.7)</td>
<td>25.5 (19.1, 33.9)</td>
<td>25.5 (19.1, 33.9)</td>
</tr>
<tr>
<td>Genotype (PiZZ)</td>
<td>4 (100%)</td>
<td>5 (100%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Adjudicated METAVIR Fibrosis Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>0 (0%)</td>
<td>1 (20%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>F2</td>
<td>1 (25%)</td>
<td>1 (20%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>F3</td>
<td>1 (25%)</td>
<td>3 (60%)</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>F4</td>
<td>2 (50%)</td>
<td>0 (0%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>FEV1 Percent Predicted</td>
<td>94 (54, 108)</td>
<td>78 (69.89)</td>
<td>82 (54, 108)</td>
</tr>
<tr>
<td>On AAT Augmentation Therapy</td>
<td>1 (25%)</td>
<td>2 (40%)</td>
<td>3 (33.3%)</td>
</tr>
</tbody>
</table>
ARO-AAT Treatment Was Associated with Reduced Serum and Intra-hepatic Z-AAT Concentration

<table>
<thead>
<tr>
<th>% Change in Intra-hepatic Z-AAT Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort 1 (Week 24)</strong></td>
</tr>
<tr>
<td>450-001</td>
</tr>
<tr>
<td>450-003</td>
</tr>
<tr>
<td>450-004</td>
</tr>
<tr>
<td>450-005</td>
</tr>
<tr>
<td><strong>Cohort 2 (Week 48)</strong></td>
</tr>
<tr>
<td>202-001</td>
</tr>
<tr>
<td>300-001</td>
</tr>
<tr>
<td>450-006</td>
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<tr>
<td>450-007</td>
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<tr>
<td>450-008</td>
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**All Median (N=9)**: -80.1
ARO-AAT Treatment was Associated with Reduced Histological Globule Burden and Improvement in Liver Fibrosis

At 48 weeks (cohort 2)
Four of the five patients achieved a 1 stage improvement in Metavir fibrosis score with no change in the other patient.

At 24 weeks (cohort 1)
Two of the 4 patients achieved improvement in Metavir Fibrosis stage, both had F4 (cirrhosis) at baseline

All 9 subjects had a decrease in histological liver globule burden
ARO-AAT, a RNAi designed to silence Z-AAT expression, was associated with:

- Rapid and Profound Reduction in serum and intrahepatic levels of Z-AAT.
- All 9 patients demonstrated a reduction in histologic globule assessment scores.
- Improvement in Fibrosis score in 6/9 patients including 2 patients with baseline cirrhosis.
- Safety profile and tolerability favorable.

- Interactions with FDA are ongoing to identify path forward toward a registration plan.

- Collaboration with Takeda and transition plan on target