ARO-AAT, an Investigational RNAi Therapeutic, Demonstrates Improvement in Liver Fibrosis with Reduction in Intra-hepatic Z-AAT Burden

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Disclosures

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• G Choudhury, W Griffiths, and C Trautwein have nothing to disclose.

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• D Christianson and B Given are former employees of Arrowhead Pharmaceuticals, Inc.

• N Rajicic, T Chang, JC Hamilton, and J San Martin are employees of Arrowhead Pharmaceuticals, Inc.

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

- **Cytoplasm**
  - Proteosomal degradation (ERAD)
  - Autophagic degradation (UPR)
- **Plasma membrane**
  - Ubiquitin
  - Lysosome
  - Autophagosome
- **Nucleus**
  - Serpin A1 (SERPINA1) mutation
  - Endoplasmic reticulum
  - PASD globules

**Inflammation and apoptosis**

**Chronic regeneration**

- Liver impairment
- Fibrosis and cirrhosis
- End-stage liver disease
ARO-AAT Inhibits Z-AAT Expression to Allow Clearance of Polymers and Globules and Improvement in Liver Health

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

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

Cytoplasm

- Plasma membrane
- Endoplasmic reticulum
- Nucleus

- Z-AAT monomer
- Z-AAT polymer
- PASD globules
- SERPINA1 mutation

- Lysosome
- Autophagosome
- Ubiquitin
- Hepatocellular injury
AROAAT-2002 Study Design

**Cohorts 1 and 1b**

- **Initial 24-Week Study:** Week 0-24
- **Treatment Extension**
- **ARO-AAT 200 mg (N=4), Cohort 1**
- **ARO-AAT 100 mg (N=4), Cohort 1b**

**Liver Biopsies**
- PiZZ
- Wk 0 → Wk 24

**Cohorts 2**

- **Initial 40-Week Study:** Week 0-48
- **Treatment Extension**
- **ARO-AAT 200 mg (N=8), Cohort 2**

**Liver Biopsies**
- PiZZ
- Wk 0 → Wk 48

**Study Visit (Week)**

- Wk 24
- Wk 48

**Q12W Dosing**
Endpoints and Interim Analysis

Endpoints
- Serum Z-AAT and liver Z-AAT (total, monomer, polymer)
- Adjudicated histology by 3 pathologists
  - PAS+D Globules
  - Fibrosis stage (METAVIR)
- Serum ALT, GGT, liver stiffness (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><strong>Age, years</strong></td>
<td>51 (20, 56)</td>
<td>62 (50, 66)</td>
<td>56 (20, 66)</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>4 (100%)</td>
<td>4 (80%)</td>
<td>8 (89%)</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>86 (71, 104)</td>
<td>84 (63, 105)</td>
<td>84.5 (63, 105)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></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><strong>Genotype (PiZZ)</strong></td>
<td>4 (100%)</td>
<td>5 (100%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td><strong>Fibrosis Stage</strong></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><strong>FEV1 Percent Predicted</strong></td>
<td>94 (54, 108)</td>
<td>78 (69.89)</td>
<td>82 (54, 108)</td>
</tr>
<tr>
<td><strong>On AAT Augmentation Therapy</strong></td>
<td>1 (25%)</td>
<td>2 (40%)</td>
<td>3 (33.3%)</td>
</tr>
</tbody>
</table>
ARO-AAT Treatment Reduced Serum and Intra-hepatic Z-AAT Concentration

% Change in Intra-hepatic Z-AAT Concentration

<table>
<thead>
<tr>
<th>Cohort 1 (Week 24)</th>
<th>Total</th>
<th>Monomer</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>450-001</td>
<td>-78.6</td>
<td>-89.8</td>
<td>-67.6</td>
</tr>
<tr>
<td>450-003</td>
<td>-95.1</td>
<td>-94.9</td>
<td>-96.6</td>
</tr>
<tr>
<td>450-004</td>
<td>-72.2</td>
<td>-86.8</td>
<td>183.7*</td>
</tr>
<tr>
<td>450-005</td>
<td>-73.4</td>
<td>-81.2</td>
<td>-71.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cohort 2 (Week 48)</th>
<th>Total</th>
<th>Monomer</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>202-001</td>
<td>-89.7</td>
<td>-96.7</td>
<td>-86.2</td>
</tr>
<tr>
<td>300-001</td>
<td>-80.1</td>
<td>-78.5</td>
<td>-80.8</td>
</tr>
<tr>
<td>450-006</td>
<td>-89.4</td>
<td>-87.8</td>
<td>-92.1</td>
</tr>
<tr>
<td>450-007</td>
<td>-77.0</td>
<td>-91.1</td>
<td>-42.2</td>
</tr>
<tr>
<td>450-008</td>
<td>-97.0</td>
<td>-97.0</td>
<td>-97.1</td>
</tr>
</tbody>
</table>

All Median (N=9) -80.1 -89.8 -80.8

* 1 subject in Cohort 1 had very low Z-AAT polymer levels at baseline that increased at Week 24
ARO-AAT Treatment Reduced Histological Globule Burden

- Histology assessed and adjudicated by 3 pathologists blinded to subject ID and time point
- Liver globule assessed semi-quantitatively (PAS+D staining): 1) Portal tract involvement, 2) periportal hepatocyte involvement, and 3) zonal location each given a score (0-3)
  - Portal tract and periportal hepatocyte involvement scoring: 0= no globules; 1= less than 1/3; 2= 1/3 to 2/3; 3= greater than 2/3
  - Zonal location: 0= no globules; 1= Zone 1; 2= Zone 1 & 2; 3= all Zones or only 2 & 3
  - Total aggregate score summarized (0-9)
ARO-AAT Treatment Improved Liver Fibrosis

- Histology assessed and adjudicated by 3 pathologists blinded to subject ID and time point
ARO-AAT Treatment Improved Biomarkers of Liver Health

% Change in Liver Stiffness and Serum Pro-C3 Concentration

<table>
<thead>
<tr>
<th>Subject Number</th>
<th>Cohort 1 (Week 24)</th>
<th>Cohort 2 (Week 48)</th>
<th>All Median (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>450-001</td>
<td>450-003</td>
<td>450-004</td>
</tr>
<tr>
<td>Liver stiffness</td>
<td>-25.8</td>
<td>-22.4</td>
<td>-0.8</td>
</tr>
<tr>
<td>Pro-C3</td>
<td>-51.4</td>
<td>5.5</td>
<td>-30.9</td>
</tr>
</tbody>
</table>

NM = not measured

* Associated with viral infections; ULN = upper limit of normal
### Summary of Safety and Adverse Events

<table>
<thead>
<tr>
<th>Subject Incidence, n (%)</th>
<th>ARO-AAT 100 mg (N=4)</th>
<th>ARO-AAT 200 mg (N=12)</th>
<th>All (N=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-emergent AEs (TEAEs)</td>
<td>4 (100%)</td>
<td>11 (92%)</td>
<td>15 (94%)</td>
</tr>
<tr>
<td>TEAEs in 2 or more subjects</td>
<td>Blood CK increased</td>
<td>1 (25%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0 (0%)</td>
<td>3 (35%)</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (50%)</td>
<td>1 (8%)</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (25%)</td>
<td>2 (17%)</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0 (0%)</td>
<td>2 (17%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (25%)</td>
<td>1 (8%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Corona virus infection</td>
<td>0 (0%)</td>
<td>2 (17%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (25%)</td>
<td>1 (8%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>1 (25%)</td>
<td>1 (8%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>0 (0%)</td>
<td>2 (17%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Sciatica</td>
<td>2 (50%)</td>
<td>0 (0%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Treatment-related TEAEs</td>
<td>3 (75%)</td>
<td>6 (50%)</td>
<td>9 (56%)</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>0 (0%)</td>
<td>3 (25%)</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>TEAEs causing deaths</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

- No TEAE-related study drug discontinuation, dose interruptions, or premature study withdrawals
- 3 SAEs reported in the 200 mg cohort
  - All moderate in severity and all resolved
  - SAE of viral myocarditis associated with EBV infection
  - SAE of diverticulitis in subject with risk factors – a 63-yr-old with PiZZ genotype and history of appendectomy
  - SAE of dyspnea in subject with medical history of non-obstructive pulmonary emphysema and delayed pulmonary care

Data Extract Date: 15 March 2021
No Clinically Meaningful Changes in FEV1 After ARO-AAT Treatment
Summary and Conclusions

In PiZZ AATD patients, treatment with ARO-AAT, an investigational RNAi therapeutic, for 24 or 48 weeks showed:

- 6 of 9 subjects with a ≥1-stage improvement in liver fibrosis, including 2 subjects who had stage F4 (cirrhosis) at baseline
- Substantial and sustained reductions in serum and intra-hepatic Z-AAT
- Decrease in histological liver globule burden
- Sustained reductions in clinically relevant biomarkers of liver health
- Acceptable safety profile
  - Generally, well tolerated after up to 1 year of treatment
  - No clinically meaningful changes in ppFEV1 or pattern of declining ppFEV1
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- **Additional Arrowhead staff**