RNA Interference Targeting Apolipoprotein C-III Results in Deep and Prolonged Reductions in Plasma Triglycerides

Christie Ballantyne MD presenting on behalf of Christian Schwabe MD and the AROAPOC31001 study investigators

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Human Genetic Validation of Apolipoprotein C-III (APOC3) as a Target for Hypertriglyceridemia, Cardiovascular Disease

- Plasma triglyceride (TG) levels are an independent risk factor for cardiovascular disease and pancreatitis
- Apolipoprotein C-III (APOC3) is a component of VLDL, chylomicrons and functions to inhibit lipoprotein lipase (LPL) and non-LPL driven TG metabolism
- APOC3 loss-of-function results in lower TG levels\(^1\),\(^2\)
- APOC3 targeted antisense oligonucleotide shown to be effective in lowering TG levels
  - toxicity profile was considered adverse, with Q1 wk dose intervals required
- APOC3 is predominantly synthesized in hepatocytes (~80-90%), an ideal target gene for RNAi therapeutic using Arrowhead’s Targeted RNAi Molecule (TRiM™) platform
  - ARO-APOC3 is a hepatocyte targeted siRNA
  - Designed to induce deep and durable gene specific silencing while avoiding off-target effects

\(^1\)Jorgensen AB et al., NEJM 2014; 371:32-41
\(^2\)TG and HDL Working Group of the Exome Sequencing Project; NEJM 2014; 371:22-31
Familial Chylomicronemia Syndrome, Severe Hypertriglyceridemia with Pancreatitis: Areas of High Unmet Medical Need

• Familial Chylomicronemia Syndrome (FCS) caused by impaired lipoprotein lipase (LPL) leading to extremely high TG levels [>880 mg/dL (10 mmol/L)]
  • Prevalence of approximately 1 in 1 million\(^1\) with increased prevalence in populations such as French Canadians (founder effect)\(^2\)
  • Symptoms include chronic daily abdominal pain, acute and chronic pancreatitis, diabetes mellitus
  • **Refractory to standard TG lowering therapies**, standard of care is very low fat (<20 g) diet

• Severe High Triglycerides (sHTG) with pancreatitis
  • Polygenic disorder exacerbated by comorbidities, diet and lifestyle
  • Prevalence of TG > 500 mg/dL (> 5.65 mmol/L) 1.7%\(^3,^4\)
  • 4% increased risk of acute pancreatitis for every 100 mg/dL (1.1 mmol/L) TG increase \(^5\)

• For both conditions adherence to current therapies including strict diet/lifestyle changes is challenging

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AROAPC31001 Study Design: Phase 1/2a clinical study

Primary Objective: Safety and Tolerability

Secondary/Exploratory Objectives: Pharmacokinetics and Pharmacodynamics
- Single and multiple dose PK of ARO-APOC3 in healthy volunteers
- Reduction in fasting serum APOC3 from baseline
- Changes in fasting serum lipids and lipoproteins

Cohort Description:

Single Dose:
- Cohorts 1-4: Normal Healthy Volunteers (NHV) with fasting TG >80 mg/dL (6 active, 4 placebo (PBO) per cohort)

Multiple Dose (2 monthly doses):
- Cohorts 1b-4b: Dose ranging in subjects with history of fasting TG ≥ 500 mg/dL
- Cohort 5: Diagnosis of Familial Chylomicronemia Syndrome or Screening TG ≥ 880 mg/dL
- Cohort 6-8: NHV, multi-dose
## Cohort 1-4 Baseline Characteristics

<table>
<thead>
<tr>
<th>Mean (range) Fasting values</th>
<th>Cohort 1 (25 mg) n = 10 (6 active: 4 PBO)</th>
<th>Cohort 2 (50 mg) n = 10 (6 active: 4 PBO)</th>
<th>Cohort 3 (100 mg) n = 10 (6 active: 4 PBO)</th>
<th>Cohort 4 (10 mg) n = 10 (6 active: 4 PBO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36 (23-51)</td>
<td>40.9 (20-61)</td>
<td>33.7 (22-65)</td>
<td>40.4 (24-62)</td>
</tr>
<tr>
<td>% Male</td>
<td>70%</td>
<td>60%</td>
<td>50%</td>
<td>70%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4 (22.8-32.0)</td>
<td>27.6 (22.3-34.1)</td>
<td>28.2 (21.0-34.1)</td>
<td>27.5 (20.6-36.6)</td>
</tr>
<tr>
<td>APOC3 (mg/dL)</td>
<td>11.5 (6.7-16.1)</td>
<td>9.2 (4.5-14.2)</td>
<td>9.7 (6.0-19.9)</td>
<td>7.7 (3.8-9.3)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>189 (80-292)</td>
<td>134 (71-230)</td>
<td>141 (80-283)</td>
<td>120 (71-204)</td>
</tr>
<tr>
<td>VLDL-C (mg/dL)</td>
<td>32 (13-51)</td>
<td>24 (13-40)</td>
<td>25 (13-51)</td>
<td>21 (13-34)</td>
</tr>
<tr>
<td>LDL-C (mg/dL) (direct assay)</td>
<td>130 (101-158)</td>
<td>126 (74-195)</td>
<td>109 (84-135)</td>
<td>112 (67-158)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>32 (13-51)</td>
<td>41 (30-54)</td>
<td>40 (30-54)</td>
<td>41 (30-57)</td>
</tr>
</tbody>
</table>
Safety (NHV cohorts 1-4)

• 40 subjects enrolled and dosed (24 active, 16 placebo)

• No Serious AEs reported

• No Severe AEs reported

• One AE of moderate transient ALT elevation (peak of 210 U/L) in subject receiving ARO-APOC3 who had elevated ALT at baseline (65 U/L), with return to baseline by end-of-study (Day 113, 45 U/L).

• No other AEs from lab abnormalities in subjects receiving drug

• 8 Local Injection Site Reactions (LISRs) – all rated mild, more common at higher doses
  • LISR defined based on specific MedDRA preferred terms with duration of at least 48 hours.
Dose Dependent Reduction of APOC3

ARO-APOC3 or Placebo given on Day 1, Mean ± SEM

- Minimal dose response seen between 25 - 100 mg, therefore added 10 mg dose level
- Mean maximum reduction from baseline in serum APOC3 levels ranged from 72% [10 mg dose] (p<0.0001) to 94% [100 mg dose] (p<0.0001)
- Reduction in serum APOC3 levels was maintained through the end of study (Week 16), with Week 16 mean reductions of 70% [25 mg dose] to 91% [100 mg dose]
• Mean maximum reduction from baseline in serum TGs ranged from 53% (77 mg/dL) [10 mg dose] (p=0.002) to 64% (92 mg/dL) [100 mg dose] (p=0.0001)

• Mean maximum reduction from baseline in serum VLDL-C ranged from 53% (16 mg/dL) [10 mg dose] (p=0.0005) to 68% (19 mg/dL) [50 mg dose] (p<0.0001)

• Reduction in serum TG and VLDL-C was maintained through the end of study, with week 16 mean reductions of 41% to 55% for TG and 42-53% for VLDL-C
Changes in LDL-C and HDL-C

ARO-APOC3 or Placebo given on Day 1, Mean ± SEM

- Mean maximum reduction from baseline in serum LDL-C of 12% (19 mg/dL) [25 mg dose] (p=0.03) to 25% (35 mg/dL) [10 mg dose] (p=0.0004)
- Dose dependent increase in serum HDL-C with mean maximum increase from baseline in serum HDL-C from 30% (13 mg/dL) [10 mg dose] (p=0.0006) to 69% (32 mg/dL) [100 mg dose] (p<0.0001)
- Serum HDL-C increases were maintained through the end of study, with week 16 mean increases of 28% (12 mg/dL) [10 mg dose] to 52% (22 mg/dL) [100 mg dose]
Conclusions

- *APOC3* loss-of-function mutations have been associated with improved CV outcomes without identified phenotypic cost
  - Lipid phenotype includes reduced triglycerides, VLDL-C and increased in HDL-C
- ARO-APOC3, a RNAi therapeutic designed to silence hepatocyte *APOC3* mRNA shows after single doses in healthy volunteers:
  - Deep and durable reductions in serum APOC3 even at 10 and 25 mg dose levels.
  - Reductions in triglycerides, VLDL-C, LDL-C and increases in HDL-C similar to those reported in GWAS studies
  - A favorable safety and tolerability profile
- Opportunity for quarterly or Q6 month dose intervals, *ideal for populations with therapy adherence issues*
- Multiple dose evaluations in patients with severe hypertriglyceridemia and/or familial chylomicronemia syndrome are underway
Thank you!