ARO-APOC3, an Investigational RNAi Therapeutic, Shows Similar Efficacy and Safety in Genetically Confirmed FCS and Non-FCS Participants with Severe Hypertriglyceridemia

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APOC3 is a key regulator of triglyceride-rich lipoproteins (TRLs) through 
lipoprotein lipase (LPL)-dependent and -independent pathways

- Familial Chylomicronemia Syndrome (FCS) is an ultra-rare genetic disease with severe 
  hypertriglyceridemia and high risk for pancreatitis
  - FCS patients harbor biallelic pathogenic DNA variants in lipolysis-associated genes

- APOC3 is a key regulator of TG metabolism
  - SHTG is characterized by excess levels of Apolipoprotein C3 (APOC3)-containing particles, such as chylomicrons or VLDL
  - Loss-of-function mutations in APOC3 are associated with lower TG, lower post-prandial lipemia and decreased 
    incidence of coronary artery disease

- ARO-APOC3 is designed to specifically target and silence the APOC3 gene, thereby reducing TG 
  levels

- ARO-APOC3 resulted in robust and sustained reductions in APOC3, TGs and Non-HDL-C with HDL-
  C increases in subjects with HTG and chylomicronemia

- The effect of ARO-APOC3 on FCS participants compared with non-FCS participants with similar 
  baseline TG levels is currently undetermined

\(^1\)Clifton P. et al, AHA Scientific Sessions 2020
ARO-APOC3 specifically targets and silences the APOC3 gene, reducing TG levels

Silencing of liver APOC3 mRNA reduces APOC3 protein in Triglyceride rich lipoproteins (TRLs)

Reduced APOC3 stimulates LPL dependent & independent clearance pathways

Decreased TRLs and remnants

Increased remnant clearance by liver
Participant Disposition and Baseline Characteristics

N=52 HTG/FCS receiving ARO-APOC3 (AROAPOC31001)

- TG ≥ 880 mg/dL
  - N=30 Subjects with TG ≥ 880 mg/dL
    - Genetic Test = No
    - N=25 non-FCS
      - N=4 FCS Biallelic Pathogenic variants (LPL)
      - Genetic Test = Yes
      - N=7 with monoallelic pathogenic variants in LPL (n=6) or APOA5 (n=1)
      - N=18 no pathogenic variants

- N=25  non-FCS

- Genetic Test = No
  - N=4 FCS Biallelic Pathogenic variants (LPL)
  - N=25  non-FCS

Parameter (SD) | FCS n=4 | Non-FCS n=25
---|---|---
Age (years) | 44.0 (13.5) | 46.8 (13.2)
Male (%) | 50 | 60
White (%) | 75 | 76
Asian (%) | 25 | 16
BMI (kg/m^2)** | 22.1 (0.8) | 30.7 (4.6)
APOC3 (mg/dL) | 48.1 (18.0) | 74.3 (22.6)
TG (mg/dL) | 1650 (1387, 4791)* | 1381 (324-5577)*
HDL-C** (mg/dL) | 12.5 (1.0) | 22.1 (7.6)
Non-HDL-C (mg/dL) | 319 (178) | 338 (209)

* TG values reported as median (min, max)
** p<0.001
Clinical Cutoff = 29 Mar 2021 (DBL)

Given similar pharmacodynamic activity, all ARO-APOC3 doses were pooled in non-FCS group.
ARO-APOC3 results in similar, sustained reduction in baseline serum APOC3 in FCS and non-FCS participants

Mean % Change from Baseline

Mean Serum APOC3 (mg/dL)
ARO-APOC3 results in similar sustained reduction of triglycerides in FCS and non-FCS participants

Median % Change from Baseline

Median and IQR Serum TG (mg/dL)
Summary Safety Findings Between FCS and Non-FCS Participants

<table>
<thead>
<tr>
<th># of Subjects Reporting ≥ 1 Event, n (%)</th>
<th>ARO-APOC3 FCS (N=4)</th>
<th>ARO-APOC3 Non-FCS (N=25)</th>
<th>All (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-emergent AEs (TEAEs) in MedDRA PT</td>
<td>3 (75%)</td>
<td>19 (76%)</td>
<td>22 (76%)</td>
</tr>
<tr>
<td>TEAEs in 2 or more subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1 (25%)</td>
<td>5 (20%)</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0 (0%)</td>
<td>4 (16%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>1 (25%)</td>
<td>2 (8%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>0 (0%)</td>
<td>2 (8%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 (0%)</td>
<td>2 (8%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1 (25%)</td>
<td>1 (4%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0 (0%)</td>
<td>2 (8%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Injection site bruising</td>
<td>1 (25%)</td>
<td>1 (4%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1 (25%)</td>
<td>1 (4%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (25%)</td>
<td>1 (4%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Treatment-related TEAEs</td>
<td>2 (50%)</td>
<td>10 (40%)</td>
<td>12 (41%)</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>0 (0%)</td>
<td>2 (8%)</td>
<td>2 (7%)</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>

- TEAEs and the safety parameters were similar and comparable with FCS compared to non-FCS subjects.

- ARO-APOC3 was generally well tolerated.

- No TEAE-related study drug discontinuation, dose interruptions, or premature study withdrawals.

- No clear pattern of an increased frequency or intensity of AEs with increasing dose level.

- 2 SAEs (chest pain and acute pancreatitis) not related to ARO-APOC3 in 2 subjects in the non-FCS group. Both subjects completed the study.
Summary

• In patients with FCS compared with non-FCS, ARO-APOC3 SC achieves similar levels of reduction of APOC3 and changes in key lipid parameters.

• In patients with FCS compared with non-FCS, safety parameters were similar and comparable.

• In patients with severe HTG (TG>880 mg/dL), ARO-APOC3 was well tolerated, and consistently decreased APOC3, TG, and non-HDL-C, and increased HDL-C, independent of underlying genetic cause of HTG.

• ARO-APOC3 may represent a promising RNAi therapeutic for the treatment of severe HTG with infrequent dosing (Q3M or greater).