RNA Interference Targeting Hepatic Angiopoietin-Like Protein 3 Results in Prolonged Reductions in Plasma Triglycerides and LDL-C in Human Subjects

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ANGPTL3 as a Target to Treat Dyslipidemia

- **Dyslipidemia** is a major risk factor for cardiovascular disease (CVD), and **residual risk of CVD** persists even with current standard of care (including PCKS9 inhibitors)

- **ANGPTL3** is a **key regulator** of lipid and lipoprotein metabolism with multiple potential nodes of action

- **Loss-of-function mutations** in **ANGPTL3** lead to low LDL-C, VLDL-C, HDL-C and triglycerides (TG)
  - Reduced risk of CVD based on GWAS
  - No known adverse phenotype associated with genetic deficiency in **ANGPTL3**
Silencing ANGPTL3 with ARO-ANG3 by RNA interference

- **ANGPTL3** is primarily synthesized in **hepatocytes**
- Ideal target for **gene silencing therapy** with a specific siRNA derived from Arrowhead’s TRiM™ platform

  - **ARO-ANG3** is a SC administered siRNA targeted at the liver, where it specifically inhibits and degrades the mRNA for ANGPTL3
  - This induces deep and durable silencing of the **ANGPTL3** gene while avoiding off-target effects

  \[ \downarrow \text{ANGPTL3 mRNA}, \downarrow \text{ANGPTL3 protein} \]
AROANG1001 Study Design: Phase 1/2a Clinical Study

Primary Objective: Safety and Tolerability

Secondary/Exploratory Objectives: PK/PD

• Single & Multiple Dose PK of ARO-ANG3 in healthy volunteers.
• Reduction in fasting serum ANGPTL3 from baseline
• Changes in fasting serum lipids and lipoprotein levels and other metabolic indices

Cohort Description:

Single Dose:
• Cohorts 1-4: Normal Healthy Volunteers (NHV) with TG >100 mg/dL and LDL-C >70 mg/dL (6 active, 4 placebo (PBO) per cohort)

Multiple Dose (2 monthly doses):
• Cohort 2b-4b: NHV, open label, 4 subjects per cohort
• Cohort 5: NAFLD, (6 active: 3 PBO)
• Cohort 6: LDL-C >70 mg/dL on stable statin regimen, (6 active: 3 PBO)
• Cohort 7, 7b, 7c: HoFH or HeFH, genetically confirmed or Dutch Lipid score of ≥ 8 with LDL-C > 100 mg/dL, (Open label, up to 6 subjects per cohort)
• Cohort 8: Severe hypertriglyceridemia, TG ≥ 500 mg/dL (Open label, up to 6 subjects)
## Cohorts 1-4: Baseline Characteristics

<table>
<thead>
<tr>
<th>Mean (range) Fasting values</th>
<th>Cohort 1 (35 mg) n = 10 (6 active: 4 PBO)</th>
<th>Cohort 2 (100 mg) n = 10 (6 active: 4 PBO)</th>
<th>Cohort 3 (200 mg) n = 10 (6 active: 4 PBO)</th>
<th>Cohort 4 (300 mg) n = 10 (6 active: 4 PBO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.1 (19-58)</td>
<td>47.4 (24-61)</td>
<td>42.2 (32-56)</td>
<td>47.4 (26-64)</td>
</tr>
<tr>
<td>% Male</td>
<td>50%</td>
<td>70%</td>
<td>80%</td>
<td>90%</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>28.1 (22.5 – 33.0)</td>
<td>27.8 (22.6 – 36.6)</td>
<td>31.4 (26.6 – 35.8)</td>
<td>26.7 (23.0 – 32.2)</td>
</tr>
<tr>
<td>ANGPTL3 (ng/mL)</td>
<td>76.2 (61-104.1)</td>
<td>75.5 (54.6-130.2)</td>
<td>83.6 (45.5-120.9)</td>
<td>73.1 (47.1-96.7)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>172 (62-779)</td>
<td>140 (80-310)</td>
<td>202 (115-354)</td>
<td>169 (97-390)</td>
</tr>
<tr>
<td>VLDL-C (mg/dL)</td>
<td>20 (12-43)*</td>
<td>28 (15-62)</td>
<td>40 (23-70)</td>
<td>34 (19-77)</td>
</tr>
<tr>
<td>LDL-C (mg/dL) (direct assay)</td>
<td>148 (54-220)</td>
<td>168 (101-263)</td>
<td>151 (85-205)</td>
<td>143 (112-217)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>48 (23-58)</td>
<td>49 (35-66)</td>
<td>43 (27-54)</td>
<td>42 (31-66)</td>
</tr>
</tbody>
</table>

* TG too high to calculate VLDL-C in a single subject, not included in mean
Durable, Dose-Dependent Reduction in ANGPTL3

ARO-ANG3 or Placebo given on Day 1

- Mean maximum reduction from baseline in ANGPTL3 (ELISA) ranged from 55% (50 ng/mL) [35 mg] (p<0.0001) to 83% (63 ng/mL) [300 mg] (p<0.0001)

- Reductions in ANGPTL3 were maintained through end of study, with week 16 mean reductions of 43% (42 ng/mL) [35 mg] to 75% (57 ng/mL) [300 mg]
Dose-Dependent Reductions in Triglycerides and VLDL-C

ARO-ANG3 or Placebo on Day 1

**Triglycerides**

- Mean maximum TG reduction from baseline of 31% (38 mg/dL) [35 mg] (p=0.06) to 66% (167 mg/dL) [200 mg] (p=0.0002)

- Mean maximum VLDL-C reduction from baseline of 30% (8 mg/dL) [35 mg] (p=0.006) to 65% (33 mg/dL) [200 mg] (p <0.0001)

- Reduction in TG and VLDL-C maintained through end of study in 200 mg and 300 mg cohorts, with week 16 mean reductions of 47% to 53% for TG, and 49% to 51% for VLDL-C
Reductions in LDL-C and HDL-C with ARO-ANG3

ARO-ANG3 or Placebo given on Day 1

- Mean maximum LDL-C reduced by 9% (16 mg/dL) [200 mg] (p=0.40) to 30% (48 mg/dL) [300 mg] (p=0.0004)
- LDL-C mean reductions at week 16 of up to 28% (46 mg/dL) [100 mg] after single dose
- Mean maximum HDL-C reduced by 8% (4 mg/dL) [35 mg] (p=0.02) to 26% (12 mg/dL) [300 mg] (p<0.0001)
- HDL-C mean reductions at week 16 of up to 16% (7 mg/dL) [200 mg]
Reductions in LDL-C with ARO-ANG3 (Single/Multiple Dose)

• Mean maximum reduction in LDL-C with 200 mg single dose blunted by two subjects in this cohort with increasing LDL-C post-dose
  • These two subjects had highest baseline triglycerides in cohort (336 and 354 mg/dL (3.8 and 4.0 mmol/L))
• Multi-dose data with 200 mg demonstrates similar reductions to 100 mg and 300 mg at 6 weeks (33-46% reduction from baseline, p<0.0001 for all dose levels)
AROANG1001 Summary Safety Results (NHV cohorts 1-4)

• 40 subjects enrolled received single ascending doses (24 active, 16 placebo)

• **No Serious AEs or drop outs** in subjects on drug

• No significant abnormalities in platelet counts or renal biochemistry

• **Two AEs** of mild transient elevations in ALT (one active, one placebo). No other AEs from lab abnormalities in subjects on drug
  
  ➢ ALT elevation in one subject on ARO-ANG3 confounded by concomitant ingestion of herbal supplement with known liver toxicity (Peak ALT 192 U/L Day 99, normal by Day 113).

• **1 mild** drug related Local Injection Site Reaction
  
  ➢ LISR defined based on MedDRA; erythema resolved after 48 hours.
Conclusions

• Loss-of-function mutations in ANGPTL3 are associated with improved CV outcomes with no adverse clinical phenotype.
  - The lipid phenotype includes reductions in triglycerides, VLDL-C, LDL-C and HDL-C.

• In normal volunteers, this single ascending dose study of ARO-ANG3, a RNAi therapeutic that specifically silences ANGPTL3 mRNA in the liver, has shown:
  - Dose-dependent reductions in fasting serum ANGPTL3.
  - Reductions in fasting TG, VLDL-C, LDL-C and HDL-C, similar to those reported in ANGPTL3 loss-of-function carriers.
  - A favorable safety and tolerability profile.

• Multi-dose studies in patients with NAFLD, hyperlipidemia while on statins, familial hypercholesterolemia, and severe hypertriglyceridemia are underway.

• ANGPTL3 inhibition is a new mechanism for potentially addressing residual risk of CVD in patients with dyslipidemias.
Thank you!