RNAi Inhibition of Angiopoietin-like Protein 3 (ANGPTL3) with ARO-ANG3 Mimics the Lipid and Lipoprotein Profile of Familial Combined Hypolipidemia

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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 PCSK9 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 genetic studies
  - No known adverse phenotype associated with genetic deficiency in **ANGPTL3**
  - Homozygotes have familial combined hypolipidemia
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 directed to hepatocytes, where it specifically degrades the mRNA for ANGPTL3
  - This induces deep and durable silencing of the ANGPTL3 gene while avoiding off-target effects
AROANG1001 First-in-Human Study Design – Healthy Volunteers

- Results from single dose cohorts presented at AHA 2019
- Subcutaneous doses of ARO-ANG3 on days 1 and 29 for repeat dose healthy volunteer cohorts
- Repeat dose patient cohorts are fully enrolled and results will be discussed in the future
## Specific Objectives

<table>
<thead>
<tr>
<th>Primary Objective</th>
<th>• Evaluate incidence of adverse events as a measure of safety and tolerability</th>
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</table>
| Secondary Objectives | • Evaluate pharmacokinetics  
                          • Determine change from baseline serum ANGPTL3 |
| Exploratory Objectives | • Evaluate fasting lipids and lipoproteins (including TG, LDL-C, Non-HDL-C, HDL-C, ApoB)  
                          • Evaluate fasting and 2-hour postprandial TGs |
## Baseline Characteristics of Repeat Dose Healthy Volunteers*

<table>
<thead>
<tr>
<th></th>
<th>Repeat Dose</th>
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<tbody>
<tr>
<td></td>
<td>100 mg Cohort 2b n = 4 (all active)</td>
</tr>
<tr>
<td><strong>Mean (Range)</strong></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.0 (20–62)</td>
</tr>
<tr>
<td>% Male</td>
<td>50%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.1 (21.7–28.0)</td>
</tr>
<tr>
<td>ANGPTL3 (ng/mL)</td>
<td>98 (92-112)</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.67 (0.81–2.31)</td>
</tr>
<tr>
<td>VLDL-C (mmol/L)</td>
<td>0.76 (0.36–1.06)</td>
</tr>
<tr>
<td>LDL-C (mmol/L) (direct assay)</td>
<td>4.09 (3.29–5.00)</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.30 (0.98–1.97)</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>6.39 (5.34–7.30)</td>
</tr>
<tr>
<td>Non-HDL-C (mmol/L)</td>
<td>5.10 (3.94–6.11)</td>
</tr>
<tr>
<td>ApoB (mmol/L)</td>
<td>1.16 (0.86 - 1.43)</td>
</tr>
</tbody>
</table>

*Inclusion criteria: TG > 1.13 mmol/L and LDL-C >1.81 mmol/L, not on statins or other lipid-lowering medications.
Repeat Dose ARO-ANG3 Demonstrated Substantial and Durable Reductions in ANGPTL3 in Healthy Volunteers Over 16 Weeks

* Maximal Mean percent (%) reductions from baseline
Repeat Dose ARO-ANG3 Demonstrated Substantial and Durable Reductions in TG in Healthy Volunteers Over 16 Weeks

* Maximal Mean percent (%) reductions from baseline
Repeat Dose ARO-ANG3 Demonstrated Reductions in LDL-C and APOB in Healthy Volunteers Over 16 Weeks

**LDL-C**

- 100 mg ARO-ANG3 (n=4)
- 200 mg ARO-ANG3 (n=4)
- 300 mg ARO-ANG3 (n=4)

**ApoB**

- 100 mg ARO-ANG3 (n=4)
- 200 mg ARO-ANG3 (n=4)
- 300 mg ARO-ANG3 (n=4)

* Maximal Mean percent (%) reductions from baseline
Repeat Dose ARO-ANG3 Demonstrated Reductions in non-HDL-C and HDL-C in Healthy Volunteers Over 16 Weeks

**Non-HDL-C**

- 100 mg ARO-ANG3 (n=4)
- 200 mg ARO-ANG3 (n=4)
- 300 mg ARO-ANG3 (n=4)

Mean (± SE) Absolute non-HDL-C Concentration (mmol/L)

- 49%* reduction in 100 mg
- 48%* reduction in 200 mg
- 54%* reduction in 300 mg

**HDL-C**

- 100 mg ARO-ANG3 (n=4)
- 200 mg ARO-ANG3 (n=4)
- 300 mg ARO-ANG3 (n=4)

Mean (± SE) Absolute HDL-C Concentration (mmol/L)

- 36%* reduction in 100 mg
- 22%* reduction in 200 mg
- 47%* reduction in 300 mg

* Maximal Mean percent (%) reductions from baseline
Reduction in fasting and postprandial TG in healthy volunteers receiving ARO-ANG3, Week 12

POST-PRANDIAL STUDY
Standardized oral fat load followed by 2-hour TG measurement.
### Safety Summary: Repeat Dose Healthy Volunteer Cohorts *

<table>
<thead>
<tr>
<th>AEs Reported in &gt; 1 subject AE Term (MedDRA Preferred Term)</th>
<th>100 mg Cohort 2b n = 4 (all active)</th>
<th>200 mg Cohort 3b n = 4 (all active)</th>
<th>300 mg Cohort 4b n = 4 (all active)</th>
<th>Total n = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>1 (25%)</td>
<td>1 (25%)</td>
<td>3 (75%)</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1 (25%)</td>
<td>1 (25%)</td>
<td>2 (50%)</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>Vascular access site bruising, Vascular access site swelling</td>
<td>1 (25%)</td>
<td>0 (0)</td>
<td>3 (75%)</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>Ligament sprain, Muscle strain, Tendon injury</td>
<td>2 (50%)</td>
<td>0 (0)</td>
<td>1 (25%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (50%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Injection site bruising, injection site discoloration</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (50%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>1 (25%)</td>
<td>1 (25%)</td>
<td>0 (0)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Abdominal pain, Abdominal pain lower</td>
<td>1 (25%)</td>
<td>0 (0)</td>
<td>1 (25%)</td>
<td>2 (17%)</td>
</tr>
</tbody>
</table>

- No reported SAEs
- No discontinuation of dosing
- No clinically significant adverse changes in platelets, total bilirubin, creatinine, transaminases
- Headache (all mild, all considered “not related” to drug) was most common AE

*Safety data through 16 weeks (end of study)*
Summary and Conclusions

• In normal volunteers, repeat doses of ARO-ANG3, an investigational RNAi therapeutic that silences ANGPTL3 mRNA, demonstrated:
  • Dose-dependent reduction in fasting ANGPTL3
  • Maximal mean reductions in fasting lipid, lipoprotein, and apolipoprotein concentrations of:
    ➢ -71% in TG
    ➢ -50% in LDL-C
    ➢ -42% in ApoB
    ➢ -34% in non-HDL-C
    ➢ -47% in HDL-C
  • Lipid, lipoprotein, and apolipoprotein reductions sustained to week 16
• ARO-ANG3 had a favorable safety and tolerability profile
• ANGPTL3 inhibition has the potential to effectively correct combined hyperlipidemia and decrease residual risk in patients with CVD on guideline-recommended standard of care