TRiM siRNA Translational Development: a Focus on ARO-ANG3 and ARO-APOC3

OPT Congress
Oligonucleotide Discovery and Delivery – March 26-27, 2019

arrowhead pharmaceuticals
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RNAi: Target the Gene Silence the Disease

Therapeutic gene silencing with RNA interference is highly precise and efficient.
 Arrowhead RNAi Platform: TRiM™: Simplicity, Specificity, and Activity

TRiM™ platform

Targeted RNAi Molecule

Simplicity, Specificity, and Activity

TRiM™ uses rules and algorithms to optimize trigger sequence

- Limit cross reactivity with off target genes
- Maximize activity
- Maximize innate stability
## Pipeline

<table>
<thead>
<tr>
<th>Competitive Position</th>
<th>Drug</th>
<th>Disease</th>
<th>Pre-clinical</th>
<th>Pre-IND</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tr>
<td>First RNAi</td>
<td>ARO-AAT</td>
<td>Alpha-1 Liver Disease</td>
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<td>Hypertriglyceridemia</td>
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<td>Cardiovascular Disease</td>
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<td>Undisclosed Target</td>
<td>ARO-AMG1</td>
<td>Cardiovascular Disease</td>
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Partnered with Janssen
Partnered with Amgen
Duration of TRIM™ in Humans - ARO-AAT Phase 1, NHV SAD/MAD study

**Single dose ARO-AAT**

- Placebo (n=17)
- 35 mg (n=4)
- 100 mg (n=4)
- 200 mg (n=4)
- 300 mg (n=4)

**Multiple dose ARO-AAT**

- Placebo (n=17)
- 100 mg (n=3)
- 200 mg (n=3)
- 300 mg (n=4)

Supports quarterly or less frequent dosing

U.S. IND filed for Phase 2/3 ARO-AAT study
ARO-AAT Summary Safety

- 45 NHV subjects received at least 1 dose

- No SAEs

- No Severe AEs

- 12% of injections resulted in AE at injection site (e.g. bruising, pain, erythema). All mild.
  - No dropouts due to injection site AEs

- No statistically significant difference in adverse FEV1 changes (active v placebo)
Cardiovascular RNAi

• We go where the technology takes us and where RNAi may have an advantage

• CV/Dyslipidemia targets optimal for siRNA
  
  • Still large unmet medical need related to residual CVD risk (after maximal lowering of LDL-C)
  
  • Niche orphan populations with inadequate treatment (FPL, FCS, HoFH)
  
  • Lipoproteins primarily synthesized in the hepatocyte yield serum biomarkers
  
  • Many targets supported by GWAS (LOF mutations seen with APOC3, ANGPTL3, LP(a), others)
Human Genetic Validation of Hypertriglyceridemia/Hyperlipidemia Targets

**Loss-of-Function Mutations in APOC3 and Risk of Ischemic Vascular Disease**


**Exome Sequencing, ANGPTL3 Mutations, and Familial Combined Hypolipidemia**

**Loss-of-Function Mutations in APOC3, Triglycerides, and Coronary Disease**

The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute

**Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease**
Mean or Median changes in lipid parameters in heterozygotes and homozygotes for APOC3 and ANGPTL3 LOF mutations versus non-carriers

<table>
<thead>
<tr>
<th>Metric (serum level)</th>
<th>APOC3 deficient heterozygote&lt;sup&gt;1&lt;/sup&gt;</th>
<th>APOC3 deficient homozygote&lt;sup&gt;2&lt;/sup&gt;</th>
<th>ANGPTL3 deficient heterozygote&lt;sup&gt;3&lt;/sup&gt;</th>
<th>ANGPTL3 deficient homozygote&lt;sup&gt;4&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>ApoC-III</td>
<td>-46%</td>
<td>-88.9%</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>ANGPTL3</td>
<td>NA</td>
<td>NA</td>
<td>-40% to -87%</td>
<td>undetectable</td>
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<tr>
<td>Triglycerides</td>
<td>-39%</td>
<td>-59.6%</td>
<td>-21.1%</td>
<td>-71.2%</td>
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<tr>
<td>LDL-C</td>
<td>-16%</td>
<td>Similar to non-carrier</td>
<td>-8.6%</td>
<td>-67.2%</td>
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<tr>
<td>HDL-C</td>
<td>+22%</td>
<td>+26.9%</td>
<td>-16.8%</td>
<td>-39.0%</td>
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<td>CAD risk</td>
<td>-40%</td>
<td>Not reported</td>
<td>-41%&lt;sup&gt;4&lt;/sup&gt;</td>
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<td>Adverse Phenotype/AEs</td>
<td>None described</td>
<td>None described</td>
<td>None described</td>
<td>None described</td>
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</table>

1. Triglyceride working group, NEJM 2014
3. Minicocci et al., J of Lipid Research 2013
4. Dewey et al, NEJM 2017
**Target Mechanism**

**APOC3 inhibition**
- Enhances peripheral LPL activity leading to enhanced VLDL clearance
- Enhanced VLDL/CM remnant particle clearance at hepatocyte

**ANGPTL3 inhibition**
- Enhances peripheral LPL activity leading to enhanced VLDL clearance
- Enhanced VLDL/CM remnant particle clearance at hepatocyte
- Reduced VLDL synthesis/assembly by hepatocyte
- Enhanced LDL-C clearance through non-LDLr mechanism
ARO-ANG3: Translational and Early Clinical Development
• 80% knockdown (KD) of ANGPTL3 with good duration at 0.5 mpk dose in WT mice
• 90%, 96% and 98% KD at 1 mpk, 2.5 mpk and 5 mpk, respectively
ANGPTL3 protein knockdown in LDLr⁻/⁻ Mice

Study design
- Mice on Western diet (n=12) or Standard chow (n=4) for 3 weeks before dosing
- ARO-ANG3 injected on Day 1 and 29 subcutaneously
- Weekly blood collection for lipid parameters and ANGPTL3 levels
- Liver Angptl3 mRNA on Day 15, 29 and 57 (Western diet) by qRT-PCR

Maximum ANGPTL3 protein reductions in ARO-ANG3 after each dose

<table>
<thead>
<tr>
<th></th>
<th>After 1st dose</th>
<th>After 2nd dose</th>
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<tbody>
<tr>
<td>Standard chow</td>
<td>95%</td>
<td>96%</td>
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<tr>
<td>Western diet</td>
<td>98%</td>
<td>99%</td>
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</table>

- Liver mRNA knockdown was 96-97% at all time points tested (relative to saline group)
- No effects on serum ANGPTL3 in Saline or Control trigger treated groups
ARO-ANG3 Reduces LDL-C and Triglycerides in \( \text{LDLr}^{-/-} \) Mice

All graphs showing group averages ± SEM

- Western Diet, Saline
- Western Diet, 3 mg/kg ARO-ANG3
- Western Diet, 3 mg/kg Control trigger
- Standard Chow, Saline
- Standard Chow, 3 mg/kg ARO-ANG3

- Mice on both Western diet and Standard chow had elevated serum lipids compared to wild-type normal mice (TGs: 35-45 mg/dL, LDL-C: 10-15 mg/dL)

Reductions in LDL-C via a non-LDLr mechanism
ARO-ANG3 in chow-fed cynomolgus monkeys: single 2 mg/kg dose

- Single 2 mg/kg ARO-ANG3 SC dose on study Day 1
- Reductions normalized to pre-dose values
- 70-90% maximum reduction in serum ANGPTL3 protein levels

Reductions in serum ANGPTL3 protein levels

Individual

Group averages ± SEM

Reductions in serum TGs

- Normal cynos have vegan like serum lipids
- Significant reductions in TGs were observed
ARO-ANG3 in HFCS-induced dyslipidemic rhesus monkeys

Reductions in serum ANGPTL3 protein levels

- SC doses on Day 1 and 29
- Over 95% maximum reductions in serum ANGPTL3 protein levels
- Normalized to pre-dose values

Reductions in serum TGs

- Animals on fructose diet for 6 weeks
- Variable diet-induced dyslipidemia
- 80% maximum mean reductions in TGs
- 30-40% reductions in LDL
• First NHV subject dosed January 2019
• Single dose safety, PD, PK in NHVs
• Multiple dose ranging in patients with:
  • NAFLD
  • Elevated LDL-C on statins
  • HoFH/HeFH
  • Elevated triglycerides (> 500mg/dL)
ARO-APOC3
Clinical Indications: Moderate to Severe Hypertriglyceridemia

Various etiologies, may be polygenic

- FCS
  - Can be monogenic: LPL, APOC2, APOA5, LMF1, GPIHBP1 and GPD1

Hegele et al., 2014
Familial Chylomicronemia Syndrome (FCS)

• FCS: Severely elevated triglycerides (often over 2,000 mg/dL)
  o Loss-of-function in gene(s) responsible for LPL dependent triglyceride clearance (LPL, APOC2, APOA5, LMF1)
  o Multiple systemic manifestations
    ▪ Recurrent abdominal pain
    ▪ Acute pancreatitis (admission, narcotics, 10% mortality)
    ▪ Neurocognitive problems
    ▪ Type 2 diabetes mellitus
    ▪ Eruptive xanthomas

• Estimated 3,000-5,000 patients worldwide

• No effective available therapy
  o Available drugs (fibrates, fish oils, niacin) ineffective as they work through LPL dependent pathway
  o Currently managed by severe dietary restrictions (< 20 grams of daily fat)
    ▪ Adherence difficult, doesn’t normalize triglycerides, only reduces pancreatitis risk
Method
APOC3 transgenic mice were given various SQ doses of ARO-APOC3 ranging from 0.01 to 3 mg/kg on study Day 1.

Results
Dose-dependent effects on depth and duration of serum ApoC3 knockdown (KD)
ARO-APOC3 Dose-response in Human-APOC3 Transgenic Mice

- Dose-dependent reductions in Triglycerides, Total Cholesterol and LDL-C, and increase in HDL-C
ARO-APOC3 in Dyslipidemic Rhesus Monkeys

- 4 mg/kg ARO-APOC3 on Day 1 and 29
- Efficacy correlates to serum APOC3 levels and severity of dyslipidemia
AROAPC31001 Clinical Study

• First subject dosed March 2019
• Single dose safety, PD and PK in NHVs
• Multiple dose ranging in patients with elevated triglycerides
• Multi-dose cohort enrolling limited number of FCS patients