BACKGROUND

- Hypertriglyceridemia and hyperlipidemia represent causative risks for atherosclerosis, and elevated triglycerides (TGs) also manifest as part of the metabolic syndrome and hepatic steatosis
- Human genetic analysis has identified that individuals with loss-of-function mutations in angiopoietin-like protein 3 (ANGPTL3) have very low plasma levels of triglycerides (TGs) and low-density lipoprotein (LDL-C), and a reduced risk of cardiovascular disease
- An RNA interference (RNAi) based therapy using Arrowhead Pharmaceuticals’ TRiM™ platform to reduce liver ANGPTL3 production by gene silencing may be an effective approach to treat dyslipidemias and metabolic diseases (AHA 2018)
- Highly potent and specific RNAi conjugates cross-reactive to human, rodent and non-human primate (NHP) ANGPTL3 transcripts were identified and studied for reductions in serum ANGPTL3 protein and liver ANGPTL3 mRNA levels
- Lead optimization studies in wild type mice and chow-fed NHPs identified development candidate ARO-ANG3
- Dyslipidemic mouse models and a dyslipidemic fructose-fed NHP model were treated with ARO-ANG3 to examine lipid lowering and metabolic effects

METHODS

- Short dsRNA targeting ANGPTL3 mRNA
- Hepatocyte ASGPR targeting ligand
- Subcutaneous (SQ) dosing
- Designed to reduce production of ANGPTL3 to potentially treat dyslipidemias
- Specific, catalytic and highly efficient

RESULTS

- **Dose response in C57BL/6J wild-type mice, N = 4/group, single SQ injection of ARO-ANG3 (Day 1)**
  - Dose-dependent reductions in serum ANGPTL3 levels
  - Day 29 hepatic ANGPTL3 mRNA correlated with serum ANGPTL3 reductions

- **Reduction of serum lipids in LDLr KO mice**
  - Mice on Western diet (n=12) or Standard chow (n=4)
  - ARO-ANG3 injected on Day 1 and 29
  - Maximum serum ANGPTL3 reductions of 89-99% (Western diet) and 95-96% (chow)
  - TGs reductions of 85% (Western diet) and 48% (chow)
  - LDL-C reductions of 48% (Western diet) and 43% (chow) through LDLr independent pathways

- **Improvements in glucose tolerance and reduction in hepatic steatosis in DIO mice**
  - 8 weeks old DIO mice on high fat diet, N=7/group
  - ARO-ANG3 injected on Days 1 and 24
  - Maximum serum ANGPTL3 reductions of 99% (after second dose)
  - Maximum TG reductions of 54% (from 70 mg/dL to 31 mg/dL)
  - Maximum LDL-C reductions of 65% (from 20 mg/dL to 7 mg/dL)

- **Efficacy in a fructose-fed dyslipidemic rhesus monkey model**
  - Animals on fructose diet for 6 weeks before dosing
  - 4 mg/kg ARO-ANG3 injected on Days 1 and 29
  - Over 95% maximum reductions in serum ANGPTL3
  - 85% maximum mean reductions in TGs
  - 20-65% max reductions in LDL-C (not shown)

CONCLUSIONS

- Our results support an ANGPTL3-targeted RNAi therapeutic as a treatment for dyslipidemia, with potential metabolic benefits
- Results in NHPs suggest human dosing intervals of once every 3 months or longer in ongoing human studies

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TRiM™ Platform

**Stabilization Chemistries**

- Short dsRNA targeting ANGPTL3 mRNA
- Hepatocyte ASGPR targeting ligand
- Subcutaneous (SQ) dosing
- Designed to reduce production of ANGPTL3 to potentially treat dyslipidemias
- Specific, catalytic and highly efficient

**Linker Chemistries**

- ASGPR-targeting ligand

**ARO-ANG3**

- Single dose duration in chow-fed cynomolgus monkeys
  - Single 2 mg/kg ARO-ANG3 injected on Day 1, N=3
  - Maximum mean serum ANGPTL3 reductions of ~60% sustained for at least 4 weeks after a single 2 mg/kg dose
  - Significant reductions in TGs were observed

- Efficacy in a fructose-fed dyslipidemic rhesus monkey model
  - Animals on fructose diet for 6 weeks before dosing
  - 4 mg/kg ARO-ANG3 (N=4), Saline (N=2), SQ injected on Days 1 and 29
  - Over 95% maximum reductions in serum ANGPTL3
  - 85% maximum mean reductions in TGs
  - 20-65% max reductions in LDL-C (not shown)