Treating hypertriglyceridemic states with RNA interference – emergence of an exciting new modality to treat cardiovascular diseases

Global Summit on Cardiology and Heart Diseases
Dubai, Sept 16-17, 2019
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COO, Arrowhead Pharmaceuticals
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Disclosures

• Dr. Given is an employee and shareholder of Arrowhead Pharmaceuticals, Inc.

• All products and indications discussed in this presentation are investigational
Outline

• Some Background on RNA Interference (RNAi)

• The CV Pipeline in RNAi

• Hypertriglyceridemia as an independent risk factor

• ApoC3 and AngPTL3 knockdown in animals and first data in humans

• Conclusions
Small Molecule Pharmaceuticals Generally Target Proteins

• The central dogma of molecular biology
  • Transcription and translation
    • the information in genes flows into proteins

• Small molecule pharmaceuticals generally target proteins
  • Enzymes
  • Receptors

• However
  • Not all proteins are targetable
  • Very difficult to address proteins in a tissue-specific manner
• In 1998, RNAi was discovered by Andrew Fire and Craig Mello.

• In 2001, siRNA was first used as a tool to silence genes in mammalian cells

• Awarded the Nobel Prize in Physiology or Medicine 2006
Basics of RNA interference (RNAi)

• Uses an endogenous host mechanism that modulates host gene expression post-transcription

• Designed for high specificity – generally one RNAi molecule will knock down only one gene

• The field has learned how to avoid unwanted stimulation of innate immunity

• In early years, the field was held back by poor delivery, currently leading companies all use ligand mediated delivery
Target the Gene, Silence the Disease

Therapeutic gene silencing with RNA interference is highly precise and efficient.
When is RNAi the Right Choice?

• When ligand-mediated or local delivery can provide beneficial/needed organ specificity:
  • Addressing the target outside of the organ of interest creates unacceptable toxicity (e.g. amiloride analogs for blocking pulmonary ENaC or other similar targets, several NASH targets, etc)

• When antibodies don’t fit the need
  • Target not accessible (various intracellular proteins)
  • The volume of protein produced is too high (Lp(a), hepcidin)
  • Target is both intracellular and extra-cellular (AngPTL3)

• When a longer (monthly or more) gap between doses delivers patient-centered benefits
  • The proposed advantage of PCSK9 RNAi drug
Components:

- Stabilization chemistries
- PK enhancers as necessary
- Linker chemistries
- Targeting ligands

Now capable of achieving deep KD in diverse tissues using subQ, iv, and inhaled administration routes.
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Public CV RNAi Programs

CV RNAi Programs

AngPTL3
APOC3
Cardiac amyloidosis
Factor 12
Lp(a)
PCSK9

Arrowhead
Arrowhead
Alnylam
Arrowhead
Amgen *
Medicines Company ^

* Licensed from Arrowhead
^ Licensed from Alnylam
Robust and Sustained LDL-C Reductions with Inclisiran*

Results to Day 360 Following One Dose

![Graph showing mean percent change in LDL-C](image)

- **300mg**: 50.9% reduction
- **300 mg**: 38.6% reduction
- **300 mg**: 19.0% reduction

P-value for all comparisons to placebo < 0.0001

Inclisiran also known as “ALN-PCSsc” and “PCSK9si”

The Medicines Company is leading and funding development of inclisiran from Phase 2 onward and will commercialize the program, if successful.

*Phase 2 study results; Ray et al., ESC, Aug 2017
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Plasma triglyceride levels are an independent risk factor for cardiovascular disease (Rosenson, ACC, 2014)

- Genetic studies support causal relationship
- Independent of LDL-C or HDL-C

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Mean or Median changes in lipid parameters after therapy and in heterozygotes and homozygotes for APOC3 and ANGPTL3 LOF mutations versus non-carriers

<table>
<thead>
<tr>
<th>Metric (serum level)</th>
<th>APOC3 deficient heterozygote¹</th>
<th>APOC3 deficient homozygote²</th>
<th>APOC3 ASO inhibition³</th>
<th>ANGPTL3 deficient heterozygote⁴</th>
<th>ANGPTL3 deficient homozygote⁴</th>
<th>ANGPTL3 ASO inhibition⁵</th>
<th>ANGPTL3 Mab Inhibition⁷ 25 mg/kg IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoC-III</td>
<td>-46%</td>
<td>-88.9%</td>
<td>-77.5%</td>
<td>NA</td>
<td>NA</td>
<td>-58.8%</td>
<td>NA</td>
</tr>
<tr>
<td>ANGPTL3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>-40% to -87%</td>
<td>undetectable</td>
<td>-84.5%</td>
<td>NA</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-39%</td>
<td>-59.6%</td>
<td>-43.8%</td>
<td>-21.1%</td>
<td>-71.2%</td>
<td>-50.4%</td>
<td>-76% i.v. (median)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-16%</td>
<td>Similar to non-carrier</td>
<td>-3.9%</td>
<td>-8.6%</td>
<td>-67.2%</td>
<td>-32.9%</td>
<td>-25%</td>
</tr>
<tr>
<td>HDL-C</td>
<td>+22%</td>
<td>+26.9%</td>
<td>+8.0%</td>
<td>-16.8%</td>
<td>-39.0%</td>
<td>-26.9%</td>
<td>-25%</td>
</tr>
<tr>
<td>CAD risk</td>
<td>-40%</td>
<td>Not reported</td>
<td>NA</td>
<td>-41%⁵</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Adverse Phenotype/AEs</td>
<td>None described</td>
<td>None described</td>
<td>Thrombocytopenia, ISRs, renal</td>
<td>None described</td>
<td>None described</td>
<td>None described</td>
<td>Elevated ALT (11% in active v 0% PBO)</td>
</tr>
</tbody>
</table>

1. Triglyceride working group, NEJM 2014
3. Graham et al., Circulation Research 2013. [Phase 1 MAD study, 400 mg dosed D1, D3, D5, D8, D15 and D22 with non-GalNac targeted ASO. Median % change 1-week after last dose in NHV population compared to baseline]
4. Minicocci et al., J of Lipid Research 2013
5. Dewey et al, NEJM 2017
6. Graham et al., NEJM 2017 [Six weekly 60 mg doses using GalNac conjugate ASO in NHV population, mean values 1 week after last dose versus baseline]
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ARO-APOC3
RNAi TRiM™ Candidate Targeting APOC3
Single-dose Study in ApoC3 Transgenic Mice

- Deep KD after a single dose
- Max KD sustained for 3 weeks
- Expected effects on lipid profile

All dosed on study day 1 at 2 mpk
Data normalized to pre-dose and D5W control

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First Look at ARO-APOC3 in Healthy Volunteers - Single 100 mg dose through week 12

**APOC3**

- Placebo (APOC3)
- 100 mg (APOC3)

**TGs**

- Placebo (TG)
- 100 mg (TG)
Top Line Safety Observations with ARO-APOC3

- No premature discontinuations in 24 healthy volunteers treated with ARO-APOC3
- No serious adverse events (such as deaths, hospitalizations, etc)
- No adverse events rated as severe
- Most common reported AEs: headache, upper respiratory infections and (all mild) injection site findings (flushing, bruising, etc)
ARO-ANG3
RNAi TRiM™ Candidate Targeting AngPTL3
ANGPTL3 Dose Response in WT mice

- Max KD on day 15
- 5 mpk close to assay detection limits

- Similar relative mRNA and protein KD on day 29
- If any, ANGPLT3 from other tissues is minimal
Mouse Disease Models Interrogated with KD of ANGPTL3

- Mouse models
  - LDL receptor knock-out (LDLr \(-/-\)) mice, western diet
  - Diet-induced obese (DIO) mice, 60% fat diet
  - Leptin receptor defective db/db mice, 60% fat diet

- All studies dosed at 3 mg/kg
## Mouse Disease Models: Pre-Dose Baseline Lipid Profiles

<table>
<thead>
<tr>
<th>Mouse Model</th>
<th>WT Normal Chow</th>
<th>DIO 10% Fat Diet</th>
<th>DIO 60% Fat Diet</th>
<th>LDLr-/- Normal Chow</th>
<th>LDLr-/- Western Diet</th>
<th>db/db 6% Fat Diet</th>
</tr>
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<tbody>
<tr>
<td># of animals</td>
<td>N= 39</td>
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<td>N=39</td>
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<td>Trig (mg/dL)</td>
<td>41 ± 6</td>
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<td>43 ± 16</td>
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</table>

All from day -1 pre-dose bleed
Effects of ANGPTL3 KD in LDLr-/- Mice

- Maximum serum ANGPTL3 reductions of 98-99% (Western diet) and 95-96% (chow)
- TGs reductions of 90% (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 8 week old DIO mice

- Maximum serum ANGPTL3 reductions of 99% (after second dose)
- Maximum TGs 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)
First Look at ARO-ANG3 in Healthy Volunteers – Single 200 mg dose through week 12

AngPTL3

- Placebo (ANGPTL3)
- 200 mg (ANGPTL3)

TGs

- Placebo (TG)
- 200 mg (TG)
Top Line Safety Observations with ARO-ANG3

- No premature discontinuations in ~36 volunteers/patients treated with ARO-ANG3
- No drug-related serious adverse events (such as deaths, hospitalizations, etc)
- No drug-related adverse events rated as severe
- Most common reported AEs: headache and upper respiratory infection
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Conclusions Regarding RNAi in CV Diseases

• Certain CV targets very well suited for RNAi

• Current advanced programs limited to hepatocyte targets
  - Once the platform is established in a cell type, simple to address most new targets
  - Rapid advances point to future programs outside the liver

• Ligand-directed RNAi offers the advantage of specificity
  - Tissue
  - Gene
  - This specificity offers potential for safety advantages

• Dosing intervals of 3-6 months expected to be the norm
**Initial Conclusions Regarding ARO-ANG3 and ARO-APOC3**

- Genetic studies indicate that plasma triglycerides are an independent risk factor for CV disease.
- Loss of function mutations of APOC3 or AngPTL3 are associated with markedly reduced triglycerides and other lipid parameters without reported adverse phenotype.
- Knockdown of APOC3 in familial chylomicronemia patients with anti-sense (data not shown) was associated with marked reductions in plasma triglycerides.
- Topline data with ARO-APOC3 in healthy volunteers indicate that it reduces plasma APOC3 and triglycerides without serious or severe adverse events.
- In animal studies AngPTL3 has endocrine effects on triglyceride and LDL-C metabolism and apparent autocrine effects on hepatic steatosis and insulin sensitivity.
  - ARO-ANG3 reduces triglycerides and LDL-C in LDL receptor knockout mice.
  - ARO-ANG3 also ameliorates steatosis and improves insulin sensitivity in diet-induced obese mice.
- Topline data with ARO-ANG3 in healthy volunteers indicate that it reduces plasma AngPTL3 and triglycerides without drug-related serious or severe adverse events.
- If accepted, more complete data will be available at AHA 2019 in November.
Comparison of Single Dose Results (APOC3)

<table>
<thead>
<tr>
<th>Mean Maximal % reduction from baseline (SD)</th>
<th>Serum ApoC3</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARO-APOC3 (100 mg)</td>
<td>94.2% (1.3)</td>
<td>63.2% (16.9)</td>
</tr>
<tr>
<td>AKCEA-APOCIII-L&lt;sub&gt;Rx&lt;/sub&gt; (60 mg)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>64.7% (21.7)</td>
<td>43% (19.7)</td>
</tr>
<tr>
<td>AKCEA-APOCIII-L&lt;sub&gt;Rx&lt;/sub&gt; (120 mg)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>91.2% (2.5)</td>
<td>79.6% (3.7)</td>
</tr>
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</table>

ARO-APOC3 inclusion criteria of TG > 80 mg/dL
*60 mg dose was the highest dose given to subjects with fasting TG ≥ 90 mg/dL
** 120 mg dose was the highest dose given to subjects with inclusion criteria of TG >200 mg/dL
<sup>1</sup>Alexander et al, Eur Heart J, 2019 40:2785-2796.
## Single Dose comparison (ANGPTL3)

<table>
<thead>
<tr>
<th>Mean Maximal % reduction from baseline (SD) [unless noted]</th>
<th>Serum ANGPTL3</th>
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<tr>
<td>ARO-ANG3 (200 mg)</td>
<td>79.4% (8.4)</td>
<td>66.2% (7.6)</td>
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<tr>
<td>AKCEA-ANGPTL3-LRx (80 mg)*1</td>
<td>61.7% (1.1)</td>
<td>56.1% (1.1)</td>
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<tr>
<td>Evinacumab (250 mg, SC)*2</td>
<td>NR**</td>
<td>51.1%*</td>
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<tr>
<td>Evinacumab (250 mg, SC)*3</td>
<td>NR**</td>
<td>55.5%*</td>
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* Inclusion criteria of TG = 90-150 mg/dL  
** Dose-dependent increases in ANGPTL3 indicating target binding of evinacumab were observed  
& Median % change  
1 Graham et al, NEJM 2017 377:222-232  
2 Dewey et al, NEJM 2017 377:211-221  
3 Ahmad et al, Circulation 2019 140: 470-486
ANGPTL3 Triggers – WT Mice and Cynos

0.5 mpk single subQ injection in wild type mice – Trigger 3.1 and 3.2

3 mpk subQ injection on days 1 and 29 in NHP – Trigger 3.1 and 3.2

- 80% KD with good duration at 0.5 mpk dose in mouse study
- Single dose at 3mpk provided 80% KD in NHP
ANGPTL3 Protein KD in db/db mice

Max KD 98%
Effects of ANGPTL3 KD on Lipid Parameters: db/db Mice

- Lipid parameters not as high as the Western diet-fed LDLr⁻/⁻ mice but 3-4 fold higher than WT mice
- ~60% reduction in TG and LDL levels
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ASOs appear to aid steatosis while Mabs do not

- Monoclonal antibodies cannot target intrahepatocyte ANGPTL3, will not improve NAFLD which is typical in metabolic syndrome in contrast to KD approach