RNAi Roundtable: ALN-PCSsc for the Treatment of Hypercholesterolemia

August 14, 2014
Welcome

- Cynthia Clayton
  Vice President, Investor Relations and Corporate Communications

Introduction

- Akshay Vaishnaw, M.D., Ph.D.
  Executive Vice President and Chief Medical Officer

Overview of Hypercholesterolemia

- Christie Ballantyne, M.D., Professor of Medicine, Physiology, and Molecular and Human Genetics, and Chief, Department of Medicine, Sections of Cardiology and Cardiovascular Research at Baylor College of Medicine

Q&A Session

- with Dr. Ballantyne

ALN-PCSsc Program

- Kevin Fitzgerald, Ph.D., Senior Director, Research
- David Kallend, MBBS, Vice President and Global Medical Director, The Medicines Company

Q&A Session
Reminders

• Event will run until ~5:00 p.m. ET
• Q&A session at end of each presentation
  » Submit questions at bottom of webcast screen
  » Questions may be submitted at any time
• Replay, slides, and audio available at www.alnylam.com
This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches, successfully demonstrate the efficacy and safety of our drug candidates, obtain, maintain and protect intellectual property, enforce our patents and defend our patent portfolio, obtain regulatory approval for products, establish and maintain business alliances; our dependence on third parties for access to intellectual property; and the outcome of litigation, as well as those risks more fully discussed in our most recent quarterly report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.
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Q&A Session
1. Liver-expressed target gene
   • Involved in disease with high unmet need
   • Validated in human genetics
   • GalNAc-siRNA enables SC dosing with wide therapeutic index

2. POC achieved in Phase 1
   • Blood-based biomarker with strong disease correlation
     » e.g., Serum TTR, thrombin generation, hemolytic activity, LDL-C, HBsAg levels

3. Definable path to approval and market
   • Established endpoints
   • Focused trial size
   • Large treatment effect
   • Collaborative approach with physicians, regulators, patient groups, and payers
# Alnylam Development Pipeline

<table>
<thead>
<tr>
<th>Discover</th>
<th>Development</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR-Mediated Amyloidosis</td>
<td>Patisiran (ALN-TTR02)</td>
<td>ALN-TTRsc</td>
<td>ALN-AT3</td>
<td>ALN-CC5</td>
</tr>
</tbody>
</table>

**Delivery Technology:**
- LNP (IV)
- Standard Template Chemistry (STC)-GalNAc Conjugate (SC)
- Enhanced Stabilization Chemistry (ESC)-GalNAc Conjugate (SC)
## Alnylam Development Pipeline

<table>
<thead>
<tr>
<th>Condition</th>
<th>Discovery</th>
<th>Development</th>
<th>Phase 1</th>
<th>Phase 2</th>
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</thead>
<tbody>
<tr>
<td>TTR-Mediated Amyloidosis</td>
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<td></td>
<td></td>
<td>Patisiran (ALN-TTR02)</td>
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<tr>
<td>Hemophilia and Rare Bleeding Disorders</td>
<td></td>
<td></td>
<td>ALN-TTRsc</td>
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</tr>
<tr>
<td>Complement-Mediated Diseases</td>
<td></td>
<td></td>
<td>ALN-CC5</td>
<td></td>
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<tr>
<td>Hepatic Porphyrias</td>
<td></td>
<td></td>
<td>ALN-AS1</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td></td>
<td>ALN-PCSsc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-1 Antitrypsin Deficiency</td>
<td></td>
<td>ALN-AAT</td>
<td></td>
<td></td>
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<tr>
<td>Hepatitis B Virus Infection</td>
<td></td>
<td>ALN-HBV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-Thalassemia and Iron-Overload Disorders</td>
<td></td>
<td>ALN-TMP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed Hyperlipidemia and Hypertriglyceridemia</td>
<td></td>
<td>ALN-ANG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td></td>
<td>ALN-AC3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional Genetic Medicine and Other Programs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Delivery Technology:**
- LNP (IV)
- Standard Template Chemistry (STC)-GalNAc Conjugate (SC)
- Enhanced Stabilization Chemistry (ESC)-GalNAc Conjugate (SC)

CTA late '14; Initial Phase 1 data mid '15
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Q&A Session
The spectrum of difficult-to-treat patients with dyslipidemia

Christie M. Ballantyne, MD
Center for Cardiovascular Disease Prevention
Methodist DeBakey Heart & Vascular Center
Baylor College of Medicine
Houston, Texas
High risk for CHD event due to extreme elevations of atherogenic lipoproteins

Relative size of high-risk populations

- HoFH
- HetFH
- Type III
- FCHL
- Lp(a)
- Polygenic HC

LDL-C, non-HDL-C, Apo B

Number at risk

11
Familial hypercholesterolemia (FH)

1 in 500 in population
Half-normal number of LDL receptors
2-fold increase in plasma LDL
Heart attacks begin at age 35 years
5% of all heart attacks under age 60 years

1 in 1 million in population
Few or no LDL receptors
6-fold increase in plasma LDL
Heart attacks in childhood

Homozygous FH

- Definition: Untreated LDL-C >13 mmol/L (500 mg/dL) with either xanthoma before 10 years of age or evidence of heterozygous FH in both parents\(^1\)

- Frequency: Estimated frequency in Germany is 1:860,000\(^2\) in Hokuriku district of Japan is 1:171,167\(^3\)

Other disorders with high LDL-C

- Familial defective apoB-100: most commonly Arg→Gln substitution at 3500, similar presentation to FH
- PCSK9 gain-of-function (proprotein convertase subtilisin/kexin 9): autosomal dominant, similar phenotype to FH
- Autosomal recessive hypercholesterolemia (ARH, gene product ARH adaptor protein): similar to HoFH if pediatric presentation, premature atherosclerosis and CVD
- Phytosterolemia (ABCG5, ABCG8): ATP-binding cassette G5, G8; autosomal recessive; very high levels of plasma sitosterol and campesterol, like FH, and recurrent joint arthritis, tuberous xanthomas; therapy: ezetimibe

### Associations with LDL-C

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Sample Size (N)</th>
<th>LDL-C Effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>mmol/L</td>
</tr>
<tr>
<td>SORT1</td>
<td>rs599839</td>
<td>116,164</td>
<td>-0.15 (-0.16, -0.14)</td>
</tr>
<tr>
<td></td>
<td>rs646776</td>
<td>111,538</td>
<td>-0.15 (-0.16, -0.16)</td>
</tr>
<tr>
<td>PCSK9</td>
<td>rs11206510</td>
<td>62,496</td>
<td>-0.08 (-0.09, -0.06)</td>
</tr>
<tr>
<td></td>
<td>rs11591147</td>
<td>140,952</td>
<td>-0.44 (-0.47, -0.41)</td>
</tr>
<tr>
<td>LDLR</td>
<td>rs2228671</td>
<td>74,661</td>
<td>-0.15 (-0.16, -0.13)</td>
</tr>
<tr>
<td></td>
<td>rs6511720</td>
<td>124,350</td>
<td>-0.19 (-0.20, -0.17)</td>
</tr>
<tr>
<td>HMGCR</td>
<td>rs12916</td>
<td>122,069</td>
<td>-0.07 (-0.08, -0.06)</td>
</tr>
<tr>
<td>ABCG8</td>
<td>rs4299376</td>
<td>107,391</td>
<td>-0.07 (-0.08, -0.06)</td>
</tr>
<tr>
<td>APOE</td>
<td>rs4420638</td>
<td>120,455</td>
<td>-0.18 (-0.20, -0.17)</td>
</tr>
</tbody>
</table>

CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; SNP, single-nucleotide polymorphism.

**Associations with CHD**

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Sample Size (N)</th>
<th>$I^2 = 87.1%, p &lt; 0.0000$</th>
<th>OR (95% CI)</th>
<th>RRR</th>
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</thead>
<tbody>
<tr>
<td>SORT1</td>
<td>rs599839</td>
<td>151,039</td>
<td></td>
<td>0.88 (0.87-0.90)</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>rs646776</td>
<td>124,040</td>
<td></td>
<td>0.88 (0.85-0.90)</td>
<td>12%</td>
</tr>
<tr>
<td>PCSK9</td>
<td>rs11206510</td>
<td>190,083</td>
<td></td>
<td>0.94 (0.92-0.97)</td>
<td>6%</td>
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<tr>
<td></td>
<td>rs11591147</td>
<td>128,244</td>
<td></td>
<td>0.73 (0.66-0.80)</td>
<td>27%</td>
</tr>
<tr>
<td>LDLR</td>
<td>rs2228671</td>
<td>83,305</td>
<td></td>
<td>0.90 (0.86-0.94)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>rs6511720</td>
<td>80,024</td>
<td></td>
<td>0.87 (0.83-0.92)</td>
<td>13%</td>
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<tr>
<td>HMGCR</td>
<td>rs12916</td>
<td>49,160</td>
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<td>0.94 (0.90-0.98)</td>
<td>6%</td>
</tr>
<tr>
<td>ABCG8</td>
<td>rs4299376</td>
<td>118,842</td>
<td></td>
<td>0.94 (0.92-0.96)</td>
<td>6%</td>
</tr>
<tr>
<td>APOE</td>
<td>rs4420638</td>
<td>78,470</td>
<td></td>
<td>0.86 (0.83-0.89)</td>
<td>14%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,003,207</td>
<td></td>
<td>0.90 (0.86-0.94)</td>
<td></td>
</tr>
</tbody>
</table>

CHD, coronary heart disease; CI, confidence interval; OR, odds ratio; RRR, relative risk reduction; SNP, single-nucleotide polymorphism

Linear effect on CHD (per unit lower LDL-C)

CHD, coronary heart disease; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; RRR, relative risk reduction

Cholesterol first isolated from gallstones

1784

Niacin first shown to lower plasma cholesterol in normal and hypercholesterolemic subjects

1955

Cholestyramine (MK-135) reported to reduce serum total cholesterol in humans by ~20%

1959

Akira Endo isolates compactin (mevastatin), paving the way for new methods of blocking HMG-CoA reductase

1973

Michael Brown and Joseph Goldstein awarded the Nobel Prize for research into cholesterol metabolism

1985

First statin (lovastatin) approved in the EU and USA

1987

The 4S study demonstrated a reduction in risk of mortality with statin treatment

1994

Ezetimibe approved in the EU and USA

2002

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HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A

Drug discovery for lipid-modifying therapy in the 20th and 21st centuries

20th Century

• SLOW

• Empiric process

• Many failures, few successes

21st Century

• Focus on human genetics

• Rare and common variants used to identify key biological pathways

• Use of biotechnology to reduce time from target identification to therapeutic trials in humans

• Target identification: epidemiology and animal studies primarily

• Time period between target identification and proof of concept in man reduced

• Target identification: epidemiology + Mendelian randomisation and human genetics

• Long gap between target selection and proof-of-concept studies in humans
Disorders with low LDL-C

1. Abetalipoproteinemia (MTP): autosomal recessive; very low total cholesterol, diarrhea, steatorrhea

2. Familial hypobetalipoproteinemia (apoB): autosomal co-dominant; near or total absence of plasma apoB and LDL-C, low VLDL and CM after fatty meal, variable presentation

3. Primary bile acid malabsorption (ileal apical sodium-dependent bile acid transporter): autosomal recessive; low plasma LDL-C, elevated fecal bile acid excretion, diarrhea, steatorrhea

4. PCSK9 deficiency (proprotein convertase subtilisin/kexin type 9): autosomal recessive; very low LDL-C (1st percentile), normal phenotype

apoB, apolipoprotein B; CM, chylomicrons; LDL-C, low-density lipoprotein cholesterol; MTP, microsomal triglyceride transfer protein; PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL, very low-density lipoprotein

Recent development of lipid-lowering therapies

- Ezetimibe approved in the EU and USA
  - 2000

- Colesevelam (a BAS) approved in the US
  - 2002

- Ezetimibe approved in the EU
  - 2004

- First publication of Phase III clinical trial data for **alirocumab** (an anti-PCSK9 mAb)
  - Mar 2012

- First publication of Phase III clinical trial data for **amg 145** (an anti-PCSK9 mAb)
  - Nov 2012

- Lomitapide (a MTP inhibitor) approved in the USA
  - Dec 2012

- Mipomersen (an antisense oligonucleotide inhibitor of ApoB-100 synthesis) approved in the USA
  - Jan 2013

- First publication of Phase III clinical trial data for **anacetrapib** (a CETP inhibitor)
  - Aug 2012

- Lomitapide approved in the EU
  - Aug 2013

ApoB, apolipoprotein B; BAS, bile acid sequestrant; CETP, cholesterol ester transfer protein; mAb, monoclonal antibody; MTP, microsomal triglyceride transfer protein; PCSK9, proprotein convertase subtilisin/kexin type 9

Human genetics – LDL vs HDL

• LDL is a straightforward target, common and rare genetic variants are associated with CHD in the expected direction

• HDL is much more complex, most variants are NOT associated with CHD unless also associated with changes in LDL-C or TGs

CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol
# Hyperlipidemia in 500 survivors of premature MI

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol alone</td>
<td>7.6%</td>
</tr>
<tr>
<td>Cholesterol &amp; triglycerides</td>
<td>7.8%</td>
</tr>
<tr>
<td>Triglycerides alone</td>
<td>15.6%</td>
</tr>
</tbody>
</table>

Definition of hyperlipidemia: ≥95% TC (285 mg/dL), ≥95% TG (165 mg/dL). Premature = age <60 years

Goldstein JL. *J Clin Invest* 1973; **52**: 1533–43.
Familial combined hyperlipidemia

- Common
- Cholesterol and/or triglyceride levels are elevated, usually to only a moderate extent, reflecting increased LDL and/or VLDL
- HDL may be low
- Characterized by overproduction of Apo B-100
- Coronary heart disease risk increased
Familial combined hyperlipidemia

- Number of genes implicated is >35 and continuing to expand
- Genes involving adipose tissue metabolism, hepatic fat and VLDL metabolism, metabolism and clearance of TG-rich lipoproteins, and clearance of LDL implicated
- Better characterization of phenotype and associated metabolic disorders in patients will help in understanding genetic basis and physiology

Genetically-altered LDL, TG, & risk for CHD

For every 1SD change (~35mg/dl) in genetically-altered LDL, 50% increase in risk for CHD

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Effect size</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_{LDL-C}$</td>
<td>0.39</td>
<td>$1 \times 10^{-22}$</td>
</tr>
<tr>
<td>$\beta_{HDL-C}$</td>
<td>0.04</td>
<td>0.32</td>
</tr>
<tr>
<td>$\beta_{TG}$</td>
<td>0.40</td>
<td>$2 \times 10^{-10}$</td>
</tr>
</tbody>
</table>
Genetically-altered LDL, TG, & risk for CHD

For every 1SD change (~35mg/dl) in genetically-altered LDL, 50% increase in risk for CHD

For every 1SD change (~90mg/dl) in genetically-altered TG, 50% increase in risk for CHD

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<td>0.04</td>
<td>0.32</td>
</tr>
<tr>
<td>$\beta_{\text{TG}}$</td>
<td>0.40</td>
<td>$2 \times 10^{-10}$</td>
</tr>
</tbody>
</table>
**APOC3 LoF carriers with markedly lower triglycerides**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Type (Carrier Frequency)</th>
<th>Mean TG in carriers (mg/dl)</th>
<th>Mean TG in non-carriers (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R19X</td>
<td>Nonsense (~1:1000)</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>IVS2+1 G&gt;A</td>
<td>Splice (~4:1000)</td>
<td>71</td>
<td>137</td>
</tr>
<tr>
<td>A43T</td>
<td>Missense (~2:1000)</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>IVS3+1G&gt;T</td>
<td>Splice (~1:1000)</td>
<td>83</td>
<td></td>
</tr>
</tbody>
</table>

APOC3 mutation carriers have 40% LOWER risk for CHD

<table>
<thead>
<tr>
<th>Study</th>
<th>OR</th>
<th>95% CI</th>
<th>P–value</th>
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</thead>
<tbody>
<tr>
<td>WHI EA</td>
<td>0.39</td>
<td>[0.14, 0.89]</td>
<td>0.019</td>
</tr>
<tr>
<td>WHI AA</td>
<td>0</td>
<td>[0, 4.3]</td>
<td>1</td>
</tr>
<tr>
<td>FHS EA</td>
<td>0</td>
<td>[0, 13]</td>
<td>1</td>
</tr>
<tr>
<td>MDC–CVA EA</td>
<td>1.7</td>
<td>[0.18, 7.1]</td>
<td>0.36</td>
</tr>
<tr>
<td>ARIC EA</td>
<td>0.59</td>
<td>[0.066, 2.5]</td>
<td>0.76</td>
</tr>
<tr>
<td>ARIC AA</td>
<td>2.4</td>
<td>[0.89, 5.7]</td>
<td>0.053</td>
</tr>
<tr>
<td>IPM EA</td>
<td>0.74</td>
<td>[0.32, 1.6]</td>
<td>0.5</td>
</tr>
<tr>
<td>IPM HA</td>
<td>0.51</td>
<td>[0.055, 2.2]</td>
<td>0.54</td>
</tr>
<tr>
<td>IPM AA</td>
<td>0.62</td>
<td>[0.12, 2]</td>
<td>0.61</td>
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<tr>
<td>ATVB+Verona EA</td>
<td>0.43</td>
<td>[0.17, 1]</td>
<td>0.043</td>
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<tr>
<td>Ottawa EA</td>
<td>0.35</td>
<td>[0.066, 1.2]</td>
<td>0.1</td>
</tr>
<tr>
<td>PROCARDIS EA</td>
<td>0.56</td>
<td>[0.23, 1.3]</td>
<td>0.17</td>
</tr>
<tr>
<td>HUNT EA</td>
<td>0.86</td>
<td>[0.24, 3]</td>
<td>1</td>
</tr>
<tr>
<td>GoDARTS CAD EA</td>
<td>0</td>
<td>[0, 1.4]</td>
<td>0.16</td>
</tr>
<tr>
<td>EPIC CAD EA</td>
<td>1</td>
<td>[0.11, 4.8]</td>
<td>1</td>
</tr>
<tr>
<td>FIA3 EA</td>
<td>0</td>
<td>[0, 0.36]</td>
<td>0.0015</td>
</tr>
<tr>
<td>German CAD EA</td>
<td>0.54</td>
<td>[0.33, 0.86]</td>
<td>0.0068</td>
</tr>
<tr>
<td>WTCCC EA</td>
<td>0.98</td>
<td>[0.47, 2]</td>
<td>1</td>
</tr>
</tbody>
</table>

All 0.6 [0.47, 0.75] 0.0000041

Gain of LPL function, gain of APOA5 function, and loss of APOC3 function reduces risk for MI
Evaluation of concepts for targeting more intensive LDL-C lowering therapy

- 1980s High cholesterol
- 1990s LDL-C + global risk
- 2000s High-dose statin for high risk
- 2014 High risk attributable to atherogenic lipoproteins
Residual risk vs risk related to atherogenic lipoproteins

• Although reductions in LDL-C are related to reductions in major vascular events (22% RRR for 1-mmol/L LDL-C reduction\(^1\)), the shape of the association may not be linear

• Patients may have a high risk for CVD events that are not driven by LDL (renal dialysis, CHF, post-ACS with low LDL-C on high-dose statin)

Despite statin therapy, many high-risk patients have marked LDL elevations

Statin discontinuation and intolerance

- Study of over 100,000 patients in 2 academic medical centers
- Over 50% of patients had temporary discontinuations
- Statin-related AEs reported in 17.4% (18,774 pts) and 59% (11,124) stopped statin
- 4545 (24%) were not rechallenged within 12 months
- 6579 (35%) rechallenged and of these, over 90% were taking a statin at 12 months

Conclusions

• The spectrum of challenging patients ranges from those with rare monogenic disorders with extremely high levels of LDL/apoB to those with more common disorders including disorders related to triglyceride rich lipoproteins.

• Benefits of LDL-C lowering are related to the absolute levels of LDL-C and the risk of CVD in the individual patient due to atherogenic lipoproteins.
Conclusions

• On maximally tolerated statin therapy, many individuals continue to have an increased risk of CVD events due to atherogenic lipoproteins.

• There are various reasons for this, ranging from resistance to therapy [some monogenic disorders, high Lp(a)] to intolerance of high-dose statins.
Conclusions: 21st Century Drug Development

• Better target identification
  – Multiple targets recently identified from common and rare disease variants in humans

• Speed of drug development greatly enhanced by advances in biotechnology
  – mAbs
  – Antisense technology and siRNA
  – More rapid small-molecule therapeutic screens

mAb, monoclonal antibody; siRNA, small interfering RNA
Welcome

- Cynthia Clayton
  Vice President, Investor Relations and Corporate Communications

Introduction

- Akshay Vaishnaw, M.D., Ph.D.
  Executive Vice President and Chief Medical Officer

Overview of Hypercholesterolemia

- Christie Ballantyne, M.D., Professor of Medicine, Physiology, and Molecular and Human Genetics, and Chief, Department of Medicine, Sections of Cardiology and Cardiovascular Research at Baylor College of Medicine

Q&A Session

- with Dr. Ballantyne

ALN-PCSsc Program

- Kevin Fitzgerald, Ph.D., Senior Director, Research
- David Kallend, MBBS, Vice President and Global Medical Director, The Medicines Company

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Q&A Session
**PCSK9 Therapeutic Hypothesis**

**PCSK9 role in both intracellular and extracellular degradation of LDLR**

**PCSK9 Synthesis Inhibitors**
Inhibit PCSK9 synthesis and both intracellular and extracellular functions

**PCSK9 Blockers**
Inhibit only extracellular functions

A. Intracellular Pathway
B. Extracellular Pathway
ALN-PCS Phase 1 Study Results
Pharmacodynamics and Clinical Efficacy

**PCSK9 knockdown and LDL-C reduction after single dose without statins**

- Randomized, placebo-controlled, single dose escalation study in healthy volunteers with elevated LDL (n=32)
- Rapid, dose-dependent, and durable knockdown of PCSK9 of up to 84% with mean lowering of 68% at 0.4 mg/kg group (p<0.0001)
- Major reductions in LDL-C of up to 50% with mean lowering of 41% at 0.4 mg/kg group (p<0.01)
- No significant decreases in HDL-C

**Graphs:**
- **PCSK9**
  - *Data for n=6 from the 0.400 mg/kg group through Day 14 only*
  - Mean Relative to Baseline and Placebo

- **LDL-C**
  - *Data for n=6 from the 0.400 mg/kg group through Day 14 only*
  - Mean Relative to Baseline and Placebo

**References:**
Fitzgerald et al., *The Lancet*; 383 (9911) 2013
Predictive Value of Baseline PCSK9 Levels

Baseline PCSK9 values predict CV events in patients on statins

Activity Independent of Baseline PCSK9 Levels

Baseline PCSK9 Distribution

All Subjects

Baseline PCSK9 (ng/mL)
SD Relative to mean

< 0.5 below (n=13)
within 0.5 (n=9)
> 0.5 above (n=10)

Fitzgerald et. al., The Lancet; 383 (9911) 2013
GalNAc-siRNA Conjugates
Systemic Subcutaneous Delivery of RNAi

Asialoglycoprotein Receptor (ASGPR)
- Highly expressed in hepatocytes
- High rate of uptake
- Recycling time ~15 minutes
- Conserved across species

GalNAc-siRNA Conjugates
- siRNA conjugated to N-acetylgalactosamine (GalNAc) ligand
- Efficient delivery to hepatocytes following subcutaneous administration
- “Enhanced stabilization chemistry” (ESC) used with ALN-AT3, ALN-PCSsc, ALN-CC5, and future programs
  - Significantly improved potency and durability compared with ALN-TTRsc
ALN-TTRsc Phase 1 Study Results
Human POC for GalNAc-siRNA Conjugates

Randomized, double-blind, placebo-controlled SAD and MAD study in healthy volunteers

- Rapid, dose-dependent, consistent, and durable knockdown of serum TTR
  - Significant knockdown of serum TTR (p<0.01) up to 94% TTR knockdown; Mean knockdown up to 92.4%
- Generally well tolerated
  - Only AEs associated with drug were generally mild ISRs, resolving within ~2 hours of onset
- Duration of effect is longer in human vs. NHP
ALN-PCSsc achieves potent PCSK9 knockdown and LDL-C lowering with SC dosing

- 2 mg/kg dose, qdx5 load; qw maintenance
- Up to 95% PCSK9 knockdown
- Up to 67% LDL-C lowering in absence of statins

![Graph showing PCSK9 knockdown and LDL-C lowering over time.](image-url)
ALN-PCSsc achieves highly durable PCSK9 knockdown and LDL-C reduction with single dose

- Single SC dose 1-10 mg/kg
- Up to 96% PCSK9 knockdown, up to 77% LDL-C lowering (in absence of statins)
- Highly durable effects, supports once-monthly or possibly once-quarterly dosing
  - >50% LDL-C lowering maintained for over 3 months in 10 mg/kg group
Initial pre-clinical safety studies support wide therapeutic index

- qWx5 dosing at 30, 100, and 300 mg/kg
- 3 Species: mouse, rat, and NHP
- NOAEL >300mg/kg in all species
  - No in-life findings
  - No significant changes in serum chemistry, ALT/AST, cytokines etc.
    - Significant reductions in LDL-C
  - No adverse histopath findings
Patient Population
- Single ascending dose (SAD): healthy subjects with elevated LDL-C
- Multiple ascending dose (MAD): healthy subjects and patients + stable statin dose

Study Size
- SAD: n~60
- MAD: n~60

Treatment Regimen
- MAD: qM SC dosing
- Placebo controlled

Endpoints
- Safety, PK, clinical activity (% reduction of LDL-C and PCSK9 compared to baseline and duration of effect)
- Other measurements, HDL-C, TGs, Total-C, ApoB, ApoA1, Lp(a)

Status
- CTA filing late 2014; initial clinical results expected mid-2015
ALN-PCSsc represents novel approach for anti-PCSK9 therapy

- Initial human POC with ALN-PCS
  - Potent PCSK9 knockdown of up to 84% and LDL-C lowering of up to 50%, in absence of statins
  - Comparable PCSK9 knockdown and LDL-C lowering in subjects with low, medium, or high baseline PCSK9 levels
  - Results published in *The Lancet*: Fitzgerald et. al, 383 (9911) 2013

- ALN-PCSsc shows potent and durable PCSK9 knockdown and LDL-C lowering in NHP
  - Up to 96% PCSK9 knockdown and up to 77% LDL-C lowering in absence of statins
  - Single dose data support qM, or possibly qQ, subcutaneous dose regimen

- ALN-PCSsc employs ESC-GalNAc-conjugate platform
  - Human translation validated in clinic with ALN-TTRsc and ALN-AT3
  - New ESC chemistry improves potency and duration

- Wide therapeutic index with NOAEL ≥300 mg/kg in initial safety studies in mouse, rat and NHP

- ALN-PCSsc CTA filing late 2014; initial clinical results expected mid-2015
Potential Differentiation Versus Anti-PCSK9 Mabs

- Clamped PCSK9 knockdown and LDL-C lowering with monthly or, possibly, quarterly SC dosing
  - Independent of baseline PCSK9 levels
  - Low SC injection volumes <1 mL
- Potential synergy with statins
## Antibody Reduction of “Free PCSK9”

### Evolocumab, 1 Week Post-Dose

**Strong initial binding to PCSK9 1 wk post dose…**

### Supplementary Table S2. Baseline unbound PCSK9 and changes one and four weeks post-administration of study drug

<table>
<thead>
<tr>
<th>Evolocumab</th>
<th>Diet only</th>
<th>Diet + Atorvastatin 10 mg/d</th>
<th>Diet + Atorvastatin 80 mg/d</th>
<th>Diet + Atorvastatin 80 mg/d + Ezetimibe 10 mg/d</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>E</td>
<td>P</td>
<td>E</td>
<td></td>
</tr>
<tr>
<td>PCSK9 Baseline, n</td>
<td>37</td>
<td>74</td>
<td>129</td>
<td>254</td>
<td>302</td>
</tr>
<tr>
<td>Baseline ng/mL mean (SE)</td>
<td>374.6 (20.4)</td>
<td>319.7 (11.3)</td>
<td>440.7 (11.9)</td>
<td>440.6 (9.2)</td>
<td>553.0 (15.2)</td>
</tr>
<tr>
<td>PCSK9 1 week post dose</td>
<td>32</td>
<td>65</td>
<td>121</td>
<td>238</td>
<td>58</td>
</tr>
<tr>
<td>PCSK9 Week 13, n</td>
<td>336.7 (21.6)</td>
<td>211.7 (7.6)</td>
<td>413.0 (10.7)</td>
<td>24.2 (5.2)</td>
<td>510.5 (16.3)</td>
</tr>
<tr>
<td>ng/mL mean (SE)</td>
<td>-2.1 (6.3)</td>
<td>-91.6 (3.0)</td>
<td>-4.5 (5.6)</td>
<td>-94.1 (1.3)</td>
<td>-5.5 (3.3)</td>
</tr>
<tr>
<td>Percent change from baseline, mean % (SE)</td>
<td>-33.9 (23.4)</td>
<td>-300.6 (15.1)</td>
<td>-24.8 (13.6)</td>
<td>-419.3 (10.8)</td>
<td>-47.2 (19.0)</td>
</tr>
<tr>
<td>Absolute change from baseline ng/mL mean (SE)</td>
<td>-92</td>
<td>-94</td>
<td>-88</td>
<td>-89</td>
<td></td>
</tr>
</tbody>
</table>
Antibody Reduction of “Free PCSK9”
Evolocumab, 4 Week Post-Dose

But, less than 50% PCSK9 bound to antibody 4 wks post-dose

<table>
<thead>
<tr>
<th>PCSK9 4 weeks post dose</th>
<th>PCSK9 Week 12, n</th>
<th>ng/mL mean (SE)</th>
<th>Percent change from baseline, mean % (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35</td>
<td>64</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>376.1 (21.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.6 (4.7)</td>
</tr>
</tbody>
</table>

% Change in Free PCSK9 (420mg dose) -45 -43 -41 -36

Cyclical LDL-C Reductions With qM Dosing

Alirocumab Results

Variation in LDL-C lowering with qM dosing for anti-PCSK9 MAB
ALN-PCSsc Clamps Both PCSK9 and LDL-C

Monthly Dosing in NHPs

ALN-PCSsc (qM, SC) achieves clamped knockdown of PCSK9 and consistent LDL-C lowering

- Up to 92% PCSK9 knockdown, up to 77% LDL-C lowering (in absence of statins)
- Data minimally support qM dose regimen; study ongoing
- Based on human translation data, expect <1 mg/kg SC doses (<1 mL)
Lack of Anti-PCSK9 MAb Synergy with Statins
Evolocumab Results

DESCARTES Phase 3 Trial:
Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES)
- Randomized, double-blind, placebo-controlled comparing evolocumab with placebo in patients with hyperlipidemia on and off statins
- Patients received study drug for 52 weeks after a run-in period of 4 to 12 weeks on background lipid therapy

Figure 2. Percent Reduction from Baseline in Low-Density Lipoprotein (LDL) Cholesterol Levels in the Evolocumab Group, as Compared with the Placebo Group, at Weeks 12 and 52, According to Background Lipid-Lowering Therapy. Values are means with lower 95% confidence limits (as indicated by T bars) in the active-treatment groups after taking into account the values in the placebo group. LDL cholesterol was measured by means of ultracentrifugation separation.

Collaboration to advance ALN-PCS program

- Create industry-leading effort for best-in-class medicine for PCSK9 antagonism
  - $25M upfront payment
  - Up to $180M Milestone payments
  - Scaled double-digit royalties on global products sales
- Alnylam to complete certain pre-clinical and Phase 1 studies
- The Medicines Company to lead and fund development from Phase 2 to commercialization
The Medicines Company

- The Medicines Company is globally established in Acute Cardiovascular Care and familiar to Cardiologists
- Expanding its cardiovascular portfolio to include ALN-PCSsc
- Experienced MDCO ALN-PCSsc team with > 15 years involvement in cardiovascular and lipid drug development including Zestril, CRESTOR, dalcetrapib, RG7652 (aPCSK9) and MDCO-216
- Currently also developing MDCO-216 (Apo A-1 Milano) for short term therapy in ACS patients
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  • David Kallend, MBBS, Vice President and Global Medical Director, The Medicines Company

Q&A Session
Upcoming RNAi Roundtables

ALN-AAT for the treatment of Alpha-1 Antitrypsin Deficiency-Associated Liver Disease
Wednesday, August 20 @ 12:30 p.m. – 1:30 p.m. ET
• Rachel Meyers, Ph.D., Vice President, Research and RNAi Lead Development
• Moderator: Akshay Vaishnaw, M.D., Ph.D., Executive Vice President and Chief Medical Officer
• Guest Speaker: David Brenner, M.D., Vice Chancellor for Health Sciences and Dean of the School of Medicine at the University of California, San Diego

ALN-AS1 for the treatment of Hepatic Porphyrias
Thursday, August 21 @ 4:00 p.m. – 5:00 p.m. ET
• Rachel Meyers, Ph.D., Vice President, Research and RNAi Lead Development
• Moderator: Barry Greene, President and Chief Operating Officer
• Guest Speaker: Karl Anderson, M.D., FACP, Professor, Departments of Preventive Medicine and Community Health (Division of Human Nutrition) and Internal Medicine (Division of Gastroenterology), and Director, Porphyria Laboratory & Center at the University of Texas Medical Branch

Replays of previous RNAi Roundtables available at www.alnylam.com/capella
Select Scientific and Clinical Meetings
Mid to Late ’14

- **High Blood Pressure Research (HBPR)**
  - September 9-12, San Francisco, CA

- **International Complement Society Workshop (ICSW)**
  - September 14-18, Rio de Janeiro, Brazil

- **American Neurological Association (ANA)**
  - October 12-14, Baltimore, MD

- **Oligonucleotide Therapeutics Society (OTS)**
  - October 12-15, San Diego, CA

- **American Heart Association (AHA)**
  - November 15-19, Chicago, IL

- **AASLD (The Liver Meeting)**
  - November 7-11, Boston, MA

- **Venue TBD**
  - November

- **American Society of Hematology (ASH)**
  - December 6-9, San Francisco, CA

* Pending acceptance of abstracts
Speaker Biographies

Akshay Vaishnaw, M.D., Ph.D.
Executive Vice President and Chief Medical Officer, Alnylam Pharmaceuticals, Inc.
Dr. Vaishnaw joined Alnylam in 2006, coming from Biogen, Inc. (now Biogen Idec Inc.), where he was most recently Senior Director, Translational Medicine. In his seven years at Biogen he was involved in many aspects of clinical research and business development, and led the effort for the approval of alefacept (Amevive™) for psoriasis. Akshay received his M.D. from the University of Wales College of Medicine, U.K., with Distinctions in Pathology and Medicine, and his Ph.D. from the University of London, U.K., in Molecular Immunology. He is a Member of the Royal College of Physicians, U.K. In addition, Akshay has published papers in leading scientific journals and authored a number of textbook chapters relating to autoimmune disease.

Christie Ballantyne, M.D.
Professor of Medicine, Physiology, and Molecular and Human Genetics, and Chief, Department of Medicine, Sections of Cardiology and Cardiovascular Research at Baylor College of Medicine
Christie M. Ballantyne, M.D., is Director of the Center for Cardiovascular Disease Prevention, Methodist DeBakey Heart Center; Chief of the Section of Cardiovascular Research, the J.S. Abercrombie Chair- Atherosclerosis and Lipoprotein Research, Chief of the Section of Cardiology, Department of Medicine, Baylor College of Medicine; Director of the Maria and Alando J. Ballantyne, M.D., Atherosclerosis Laboratory; Professor of Medicine, Professor of Genetics, Professor of Physiology with a joint appointment in Pediatrics, Baylor College of Medicine; and Director, Lipid Metabolism and Atherosclerosis Clinic, The Methodist Hospital, Houston, Texas. He received his Doctor of Medicine from Baylor College of Medicine, and his postgraduate training included an internal medicine residency at The University of Texas Southwestern Medical School, Dallas, Texas, a cardiology fellowship at Baylor College of Medicine, and an American Heart Association/Bugher Foundation Fellowship at the Howard Hughes Medical Institute and Institute for Molecular Genetics at Baylor. Dr. Ballantyne is a Fellow of the American Association for the Advancement of Science, member of the American Society for Clinical Investigation, Fellow of the American College of Cardiology, and Fellow of the American College of Physicians. He received the American College of Cardiology Award as the 2013 Distinguished Scientist. He previously served as governor of the Texas Chapter of the American College of Cardiology and president of the Houston Chapter of the American Heart Association. Dr. Ballantyne has been the recipient of numerous study grants, including an American Heart Association Established Investigator Award and several NIH grants to study leukocyte–endothelial adhesion molecules and novel biomarkers for atherosclerosis. He has been a member of numerous steering committees for multicenter trials, including the Atherosclerosis Risk in Communities (ARIC) study, Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT), A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID),DAL Outcomes, and has also participated as a member of several Data and Safety Monitoring Boards. Dr. Ballantyne is Editorial Director for www.lipidsonline.org. He has published extensively and has spoken nationally and internationally on lipids, atherosclerosis, and inflammation. Dr. Ballantyne's research interests include the pathophysiology of atherosclerosis, with an emphasis on monocyte activation and adhesion. His clinical interests include preventive cardiology, lipids, metabolic syndrome, atherosclerosis, genetics, and coronary artery disease.
Kevin Fitzgerald, Ph.D.
**Senior Director, Research, Alnylam Pharmaceuticals, Inc.**
Kevin Fitzgerald joined Alnylam in 2005. He has held various responsibilities while at Alnylam from Project Leader for PCSK9 to Head of Delivery and more recently has been responsible for the pre-clinical to Phase 1 pipeline. Before joining Alnylam, Kevin spent 7 years at Bristol Myers Squibb where he worked to help found the Dept. of Genomics as a Group Leader. While at Bristol Myers Squibb he was involved in the validation of novel targets for oncology and metabolic disease and was responsible for ascertaining the mechanism of action of compounds whose activities were unknown. His group was the first to show Notch pathway inhibition by gamma-secretase inhibitors. While at BMS Kevin worked on several programs that are continuing their way through clinical trials, and Dacatinib, which was repurposed from immunology to become a commercial oncology drug. Kevin received his B.S. in genetics at Cornell and his Ph.D. in Molecular Biology from Princeton, and trained as a post-doctoral fellow in oncology at Harvard Medical School, where he was supported by the Leukemia Society. He has co-authored more than 20 papers describing work utilizing RNAi technologies, including the 2013 *New England Journal of Medicine* paper describing clinical trials with RNAi therapeutics for the treatment of TTR-mediated amyloidosis, and was the lead author on a paper describing a clinical trial with an RNAi therapeutic targeting PCSK9 that was published in *The Lancet*.

David Kallend, MBBS
**Vice President and Global Medical Director, The Medicines Company**
Following graduation from Kings College Hospital School of Medicine in London, Dr. David Kallend worked in various hospital departments in the UK, predominantly at the Royal Postgraduate Medical School Hammersmith Hospital, London, where his final post was Research Fellow in the Department of Surgery. In 1995 he joined the pharmaceutical industry. He initially worked as an International Clinical Research Physician on imaging studies for Schering AG in Berlin, predominantly in the area of magnetic resonance contrast media for clinical imaging. Following this he joined AstraZeneca in 1998, based in the UK, working mainly on the development of rosuvastatin from Phase II to Phase IV and the post-approval phase. He was also involved as an advisor to other cardiovascular programs and collaborations. From 2005 to 2012 he was the Global Clinical Leader and a Group Medical Director for dalcetrapib at Roche in Switzerland. In this role he was responsible for the clinical development plan during Phase II and Phase III. He was also an advisor for other lipid programmes including the aPCSK9 mAb and various due diligence procedures. His current role is Vice President and Global Medical Director for the early development lipid programs, Apo A-1 Milano and aPCSK9, at The Medicines Company. During these last 19 years he has been involved with many developments and clinical studies in the cardiovascular area and several regulatory approvals worldwide.
Thank You

www.alnylam.com