Alnylam Pharmaceuticals
R&D Day

STAR
CARDIO-METABOLIC DISEASE

December 12, 2014
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.
Daniel Rader, M.D.
Chair, Department of Genetics,
Perelman School of Medicine,
University of Pennsylvania
Cardiometabolic Disease: an Epidemic

Insulin resistance
Type 2 diabetes
Inflammation
Hypertension
Dyslipidemia
Fatty liver
Cardiovascular disease
Prevalence of obesity (% adults with BMI $> 30$)
Body fat distribution

Visceral fat
Subcutaneous fat

Obese
Lean

National Geographic; Aug 2004
Diseases associated with obesity

- Diabetes
- Dyslipidemia
- Hypertension
- Heart disease
- Stroke
- Sleep apnea
- Hypoventilation
- Asthma
- GERD
- NAFLD
- Gall stones
- Gout
- Osteoarthritis
- PCOS
- Infertility

- Thrombophlebitis
- Lymphedema
- Psoriasis
- Depression
- Pseudotumor cerebri
- Dementia
- Cancer (breast, endometrium, ovary, prostate, colon, esophagus, stomach, kidney, pancreas)

**Type 2 diabetes**

**Coronary Heart Disease**


*Folsom et al. Arch Intern Med 2000;160:2117. The Iowa Women’s Health Study*
Hospitalization Costs for Chronic Complications of Diabetes in the US

- Cardiovascular disease: CVD accounts for 64% of total costs
- Total costs: 12 billion US $

- Others
- Neurologic disease
- Peripheral vascular disease
- Renal disease
- Ophthalmic disease
Dyslipidemia and coronary disease

TG, CE → LDL → TG-rich lipoproteins → Lp(a) → A-I → CE → HDL
The Liver LDL Receptor regulates plasma LDL levels
PCSK9 is a liver-derived protein that regulates LDL uptake and is a major target for therapeutic inhibition.
Triglyceride-rich lipoproteins are an important cause of cardiovascular disease.
Multiple liver-derived proteins influence triglyceride metabolism.
Non-alcoholic fatty liver disease (NAFLD)

- Normal
- Steatosis (fatty liver)
- Steatohepatitis (inflammation and stellate cell activation)
- Fibrosis (collagen deposition)
- NASH
- Cirrhosis
The Burden of NAFLD in the US

Mortality in NAFLD

18-year Mortality

- **NAFL**: 2.7%
- **NASH**: 17.5%

Causes:
1. CV
2. Cancer
3. Liver

Pathophysiology of NAFLD and Cardiometabolic disease

Anstee, Nature Reviews Gastro and Hepatol 2013
The Liver is a Central Mediator of and Therapeutic Target for Cardiometabolic Diseases

- Angiotensin-Renin system
- LDL/HDL
- FFAs
- TGs
- Lipid Storage
- NAFLD/NASH
- Cardiovascular Disease
- LDL/HDL Clearance
- Intra-abdominal Obesity
- GI Tract
- Nutrients
- Glucose
- Fructose
- Insulin
- Type 2 Diabetes
- Glucotoxicity
- Insulin Resistance
- Inflammation
- Hypertension
- Glucose
- Gluconeogenesis
- GI Tract
- Pancreas
- Retinopathy
- Nephropathy
- Neuropathy
- LDL/HDL
- Fructose
- Lipid Storage

- GI Tract
- Pancreas
- Retinopathy
- Nephropathy
- Neuropathy
- LDL/HDL
Rachel Meyers, Ph.D.
Vice President, Research and RNAi Lead Development

Cardio-Metabolic Pipeline
### Alnylam Development Pipeline

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<th>Category</th>
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Alnylam RNAi Therapeutics Strategy
A Reproducible and Modular Path for Innovative Medicines

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
Emerging Profile for RNAi Therapeutics
Cardio-Metabolic Disease

Emerging profile for ESC-GalNAc-siRNA conjugates

- Attractive pharmacologic properties
  - Subcutaneous dose administration
  - High potency with microgram/kg (mcg/kg) doses
  - Low volume per injection, <1 mL
  - Durability for monthly (qM) and possibly quarterly (qQ) dose frequency

- Competitive profile with RNAi mechanism
  - Block synthesis of disease-causing protein
  - Efficacy independent of target protein blood levels
  - Clamped knockdown with low inter-individual variability

- Well tolerated and wide therapeutic index

Unique opportunity for cardio-metabolic disease

- Growing human genetics data expands accessible target space
  - Large populations continue to be genetically segmented
- Potential to address more common diseases impacting millions of people
- Improved compliance expected due to infrequent dosing
- Dual-targeting possible
Human Liver
Central Mediator of Multiple Inter-Related Cardio-Metabolic Diseases

- Hypertension
- Angiotensin-Renin system
- NAFLD/NASH
- Cardiovascular Disease
- LDL/HDL
- Intra-abdominal Obesity
- GI Tract

- Insulin Resistance
- Gluconeogenesis
- Fructose
- Lipid Storage
- Nutrients
- LDL/HDL Clearance

- Type 2 Diabetes
- Glucotoxicity
- Insulin
- Glucose
- FFAs
- TGs

- Inflammation
- Retinopathy
- Nephropathy
- Neuropathy
- Pancreas

- Glucotoxicity
- Insulin Resistance
- Type 2 Diabetes
Dyslipidemia Pathophysiology and Disease Burden

- Key Contributors
  - Genetic factors, obesity, poor nutrition, physical inactivity
- Cardiovascular disease leading cause of mortality in U.S.
- Dyslipidemia patient population growing rapidly, outpacing population growth

![Altered Lipid Metabolism](image)

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Unmet need in hypercholesterolemia
- Elevated LDL-C validated risk factor for CVD
- 34 million Americans have hypercholesterolemia (> 240 mg/dL)
- Recent clinical studies
  - Many patients on statins do not meet LDL-C goal
  - Lower LDL-C is better
- Multiple genetically defined patient subgroups

PCSK9 is a genetically validated target
- GOF mutations associated with hypercholesterolemia and premature CHD
- LOF mutations associated with hypocholesterolemia and decreased CHD risk

Plasma LDL Cholesterol (mg/dl)

Frequency (%)

Coronary Heart Disease (%)

PCSK9 Therapeutic Hypothesis

MAbs are PCSK9 blockers
Bind 1:1 to PCSK9 protein – sensitive to plasma levels

RNAi therapeutics are PCSK9 synthesis inhibitors
Catalytic degradation of PCSK9 mRNA – independent of plasma levels
**ALN-PCS02 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
  - 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)

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; 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

**PCSK9**

- % PCSK9 Knockdown (relative to pre-bleed)
- ALN-PCSsc (mg/kg) vs. Days

**LDL-C**

- % LDL-C Lowering (relative to pre-bleed)
- ALN-PCSsc (mg/kg) vs. Days

Fitzgerald, AHA, Nov 2014
Potent and stable PCSK9 knockdown and LDL-C lowering with monthly SC dosing

- Monthly SC dose regimen
  - 6 mg/kg 1st dose, 3 mg/kg monthly maintenance
- Up to 92% PCSK9 knockdown, up to 77% LDL-C lowering; absence of statins
- Clamped knockdown of PCSK9 and reduction in LDL-C levels with monthly maintenance dosing for over 6 months
Differentiation for ALN-PCSsc
- Clamps PCSK9 knockdown and LDL-C lowering with monthly or, possibly quarterly SC dosing
  » Independent of baseline or fluctuating PCSK9 levels
- Potential for synergy with statins
  » Statins upregulate PCSK9 and compromise MAb efficacy

Rebound in LDL-C with qM dosing for anti-PCSK9 MAb

McKenney et. al., JACC, 59, No.25, 2012
ALN-PCSsc Phase 1 Study

Study Design
- Randomized, single-blind, placebo-controlled, single ascending dose (SAD) and multi-dose (MD), subcutaneous dose-escalation study
- Up to 76 volunteer subjects with elevated baseline LDL-C (≥100 mg/dL)
  - MD phase to also include subjects both on and off statin co-medication
- 3:1, ALN-PCSsc vs. placebo

Treatment Regimen
- SD or MD (qM x 2)

Study Objectives
- Primary: safety and tolerability of ALN-PCSsc
- Secondary: PK, clinical activity (% reduction of LDL-C and knockdown of PCSK9 compared to baseline)

Status
- Phase 1 started
- Initial clinical data expected mid-2015
Unmet need in hypertriglyceridemia

- >50M in U.S. have high triglycerides (>200 mg/dL)
  - >3M have very high triglycerides (>500 mg/dL)
- Additional opportunity in ultra-rare orphan condition in people lacking properly functioning lipoprotein lipase (LPL)
  - ~1,000 Patients with Familial Chylomicronemia Syndrome

APOC3 inhibits lipoprotein lipase to prevent triglyceride hydrolysis

- Loss-of-function individuals have lower triglyceride levels, lower rates of coronary artery calcification, and CVD risk
- Pro-inflammatory effects on vascular endothelium
- Primarily expressed in liver

Crosby NEJM 371:22 (2014)
ALN-AC3 inhibits ApoC3 and reduces triglycerides

- 94% reduction of human serum ApoC3 at 3 mg/kg
  - Durable effect
- Up to 50% lowering of triglycerides in db/db mouse model of hyperlipidemia

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Human ApoC3 Protein

- ALN-AC3 q2W x 5

Triglyceride Lowering

- 1.25 mg/kg
- 2.5 mg/kg
- 5.0 mg/kg

Days

% ApoC3 Knockdown (Relative to Pre-dose)

% TG Lowering (Relative to Pre-dose)

Fitzgerald, ATVB, May 2014
ANGPTL3 is genetically validated target
- Functions as lipase inhibitor
- Loss of function ANGPTL3 mutations associated with combined hypolipidemia
  - Increased LPL activity, increased insulin sensitivity
  - Extremely low LDL-C, HDL-C, and triglycerides
  - Decreased free fatty acids

Musunuru et al., NEJM (2010)
ALN-ANG inhibits ANGPTL3 and reduces circulating lipids in ob/ob mice

- Up to 99% lowering of serum ANGPTL3
- Up to 80% reductions in triglycerides and LDL-C
Hypertension (HTN)
Significant Unmet Needs in Specific Populations

- Highly prevalent disease
  » Compliance is area of high unmet need
- High unmet need in preeclampsia for safe and effective therapy
  » >500,000 U.S./EU pregnancies complicated by hypertension
  » Preeclampsia in >200,000/year
    - 10-20% of maternal or fetal perinatal deaths
    - Premature delivery associated with neonatal intensive care, risk of morbidity and mortality
- Opportunity for RNAi therapeutic targeting angiotensinogen in maternal liver
  » Pharmacologically validated pathway
  » Control hypertension, preeclamptic symptoms
  » Maintain pregnancy, extend gestation, and avoid premature delivery
  » RNAi therapeutic does not cross placenta, avoiding fetal exposure

ALN-AGT improves maternal preeclamptic symptoms without fetal exposure

- >90% Silencing maternal AGT
  » No fetal exposure of drug
- Improves hypertension with ~20 mmHg decrease in mean arterial pressure
- Improves preeclamptic symptoms
  » >80% reduction in proteinuria
  » >75% reduction in maternal VEGF receptor-1 (FLT1)
- Significant improvements in fetal outcomes

**Albuminuria**

- PE Control
- PE RNAi

**Fetal Weight**

- PE Control
- PE RNAi

**Tissue Exposure**

- Maternal Liver: 25,712 ng siRNA/g tissue
- Placenta: 97 ng siRNA/g tissue
- Fetal Liver: <LOD (Limit of Detection)
NASH is progressive fibrotic liver disease
- Leads to cirrhosis and liver failure
- ~1M diagnosed patients in U.S.
  - NASH growth >> population growth
    - Fueled by expansion of metabolic co-morbidities
  - Availability of therapy and novel diagnostics will expand diagnosed patients in future
    - Estimated ~3M patients by 2030
- Third most common cause of liver transplantation in U.S., and growing

Therapeutic options needed
- Currently no approved therapies
- Several agents in development but unmet needs will remain

Number of liver targets for RNAi therapeutics
- Multiple Alnylam opportunities being pursued
Type 2 Diabetes one of fastest growing health burdens in established markets

- WW prevalence ~370M by 2030
  » ~$245B costs in U.S. in 2012
- Multiple disease complications
  » Increased CV risk, renal disease, retinopathies, neuropathies
- Growth due to aging population, lifestyle choices, co-morbid conditions

Opportunity clearly defined

- Novel therapeutics should deliver demonstrable “dual benefit”
- Glucose control plus other benefit, such as weight loss

Number of liver targets for RNAi therapeutics

- Multiple Alnylam opportunities being pursued
  » Includes dual-targeting

Boyle. Popul Health Metr 8:29; (2010); American Diabetes Association The Cost of Diabetes, (2012)
Significant opportunity for RNAi therapeutics as transformative medicines in cardio-metabolic diseases

- High unmet medical need in multiple patient segments
  - Dyslipidemia, hypertension, NASH, and type 2 diabetes
- Many important hepatocyte-expressed targets
- Increasing power of human genetics fueling more opportunities
- Emerging profile for ESC-GalNAc-siRNA highly attractive
  - Potent and durable, with very wide therapeutic index
  - Durability supports qM to qQ subcutaneous dose regimens
  - Ability to achieve dual targeting
Alnylam Cardio-Metabolic Disease STAr advancing multiple programs

- Established human POC with RNAi therapeutics
  - ALN-PCS02: robust knockdown of PCSK9 and reduction of LDL-C in Phase 1 study
- ALN-PCSsc in Phase 1 trial for hypercholesterolemia
  - Initial data expected in mid ’15
  - Partnered with The Medicines Company
- Additional programs in development for dyslipidemia and hypertensive disorders of pregnancy
  - Includes ALN-AC3, ALN-ANG, and ALN-AGT
- Multiple additional pipeline programs
  - Expect ~1 IND/ year

Represents new opportunities for partnership

- Alnylam to retain meaningful product rights in core markets
- Leverage partner for expanded effort and geographic scope